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The *Journal of Associated Medical Sciences* belongs to the Faculty of Associated Medical Sciences (AMS), Chiang Mai University, Thailand. The journal aims explicitly to provide a platform for medical technologists, radiologic technologists, occupational therapists, physical therapists, speech-language pathologists, and other related professionals to distribute, share, and discuss their research findings, inventions, and innovations in the areas of:

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2. Radiologic Technology
3. Occupational Therapy
4. Physical Therapy
5. Communication Disorders
6. Other related fields

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The validity and reliability of modified cough transport outcome using slower airflow for assessing mucus viscoelasticity

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ABSTRACT

Background: The cough transportability technique reflects changes in mucus rheology. However, the necessity of high airflow rates, such as 8 L/s, to carry out this technique limits its utility, as specialized setups or equipment are required.

Objective: This study aims to identify practical alternatives to higher airflow rates and utilize easily accessible equipment, such as mechanical air pumps (2 L/s).

Materials and methods: Mucus simulant gel (MSG) of 4 viscoelasticity and sputum from patients with bronchiectasis were collected and prepared. All samples underwent standard airflow cough transport (sCT) and modified cough transport (mCT). Additionally, three rounds of each MSG and two rounds of sputum underwent mCT.

Results: A Pearson correlation analysis between mCT and sCT revealed very high ($r=0.986$, $p=0.014$) and high ($r=0.771$, $p<0.001$) in the MSG and the sputum of bronchiectasis patients, respectively. The test-retest reliability of mCT revealed ICCs of 0.997 and 0.926 in the MSG and sputum of patients with bronchiectasis, respectively.

Conclusion: mCT could be an alternative to sCT, offering a more accessible option for conducting cough transportability assessments to reflect changes in mucus rheology in airway clearance research.

Introduction

Increasing the viscoelasticity of mucus harms secretion clearance and is one of the most common problems in chronic respiratory diseases like bronchiectasis.^{1,2} In patients with bronchiectasis, the sputum viscoelasticity usually changes due to response to a vicious cycle of infection and inflammation.³ Therefore, airway clearance interventions focus on reducing secretion viscoelasticity. The challenge of measuring the viscoelastic properties of mucus persists, primarily due to its shear-thinning nature, meaning its viscoelasticity changes with the applied stress.⁴ Consequently, not all equipment designed for assessing viscoelasticity is suitable for evaluating

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respiratory mucus viscoelasticity, leading to a limited availability of appropriate equipment for this purpose. Additionally, accessing the current equipment used to measure magnetic rheometer,^{5,6} is hampered by expensive costs and the need for specialized synthesis, placing further limitations on their practical application.

Agarwal *et al.* and King *et al.* studied the effects of cough on mucus and mucus effects on cough using the simulated cough machine with high flow rates (at least 8-11 L/s) used as a standard procedure.^{9,10} The viscoelasticity of mucus affects cough clearance. In other words, the higher the mucus viscoelasticity, the less cough clearance is achieved.^{11,12} Therefore, this concept has been developed to measure cough transportability outcomes in the research area, especially the airway clearance effectiveness research, aiming to indirectly investigate changes in mucus viscoelasticity. It predominantly adapts the protocols proposed by Agarwal *et al.* and King *et al.*^{9,10}

The cough transportability outcome measurement is simple, cost-effective, and possible to set up. However, the requirement for generating a high flow rate, often achieved through sophisticated technology like pressurized air systems, restricts its application in research. Exploring alternatives with slower airflow rates using more readily available equipment would be advantageous, providing researchers with an accessible and cost-effective method to assess changes in viscoelasticity. Low airflow can be generated with easily accessible equipment such as an air compression pump or devices commonly available in clinical settings, such as self-inflating bags, oxygen tanks, or medical gas pipelines. This approach also reduces the risk of aerosol transmission.

Therefore, this study aimed to investigate potential alternatives utilizing a lower airflow rate (2 L/s) and easily accessible equipment. This entailed examining psychometric properties, particularly validity compared to the standard airflow (8 L/s), and the reliability of synthetic mucus simulant gel (MSG) and sputum obtained from individuals with bronchiectasis.

Materials and methods

This study was approved by the Center of Ethics in Human Research. Patients with bronchiectasis provided informed consent. The MSG and sputum of patients with bronchiectasis were subjected to a reliability and validity analysis study.

The protocol for cough transportability was adapted from King *et al.*¹⁰ Validity testing for MSG and sputum involved the application of two cough transport protocols: modified cough transport (mCT) and standard airflow cough transport (sCT). This was done with samples of MSG of four viscoelasticity levels (testing of 3 times and used average value of each level) and 45 samples of sputum from patients with bronchiectasis. To determine mCT's test-retest reliability, samples of MSG of four viscoelasticity levels underwent three rounds of mCT, and 30 sputum samples underwent two rounds of mCT.

Mucus simulant gel (MSG)

Mucus simulants were prepared for this study using a method similar to previous studies. Locust bean gum (LBG) and sodium tetraborate ($\text{Na}_2\text{B}_4\text{O}_7$), commonly known as borax, created MSG.^{10,13} To prepare MSG, 0.38 gm of LBG powder was dissolved in 100 mL of hot deionized water. While the LBG solution was still hot, different volumes (3 mL, 6 mL, 9 mL, and 12 mL) of 0.02 M $\text{Na}_2\text{B}_4\text{O}_7$ (2% molecular weight of borax in 1000 mL of water) were added to each of the samples and stirred to obtain samples of mucus simulants with four viscoelasticity levels. The samples containing 3 mL of borax + LBG represented normal mucus. They were labeled low viscosity, while the samples containing 12 mL of borax + LBG represented mucus in severe lung disease and were labeled high viscosity.^{13,14} The other groups containing 6 mL of borax + LBG and 9 mL of borax + LBG were labeled median 1 and median 2 viscosities, respectively. All samples were prepared before each experiment and used on the same day. The samples were placed in a 37 °C water bath for 20 min immediately before conducting experiments.

Sputum samples

Different conditions of sputum samples, including pre-airway clearance session, during airway clearance session, and post-airway clearance session from ten patients, were collected for three days.

The sputum samples were centrifuged (4700 rpm at 4 °C for 20 min), and remove the supernatant saliva. The saliva-free sputum samples were placed in a water bath at 37 °C for 20 min before undergoing cough transport.

Trachea model

Rigid clear Plexiglas with a rectangular cross-section of 1x2x35 cm was used for constructing a trachea model. The base and sides of the Plexiglas were glued to form a U-shaped tube, and the unglued top was secured with transparent tape during the experiments.¹⁰ A bacterial filter was attached to the distal end of the model to prevent aerosol spreading.

Standard airflow cough transport (sCT)

Regarding airflow in sCT, a motorized fan (five blades; speed ratio = 4500 rpm/volt) was connected to a BIOPAC airflow sensor and the model trachea. The flow rate was manually adjusted using an electronic speed controller set to 8 L/sec¹⁵ for 1 sec.¹⁶ In each measurement, 0.5 mL of MSG or sputum, with a depth of 0.5 mm,⁸ was placed at the bottom of the trachea model and two non-soluble light particles were loaded onto the mucus.

Modified cough transport (mCT)

Regarding airflow in mCT, the mechanical air pump was connected to the BIOPAC airflow sensor and model trachea. The flow rate was manually adjusted using a valve set to 2 L/sec for 6 sec. In each measurement, 2 mL of MSG or sputum, with a depth of 1 mm, was placed at

the bottom of the trachea model, and 2 non-soluble light particles were loaded onto the mucus.

Cough transport procedures and measurements

Air was blown into the trachea model. The experiment was recorded using an iPhone 12 Pro Max (12 MP 4,032×3,024). The data were extracted from the recorded video using Adobe Premiere software by measuring the maximum displacement of the particles on the mucus in centimeters (Figure 1).

Data analysis

The distribution of the data was assessed using the Shapiro-Wilk test. Validity was determined through Pearson correlation.¹⁷ The test-retest reliability was assessed using the intraclass correlation coefficient (ICC (3,1)). The Intraclass Correlation Coefficient (ICC) ranges from 0 to 1, with values under 0.5 indicating poor reliability, between 0.5 and 0.75 indicating moderate reliability, 0.75 and 0.9 indicating good reliability, and values above 0.9 indicating excellent reliability.¹⁷ SPSS version 23 was used to analyze all data.

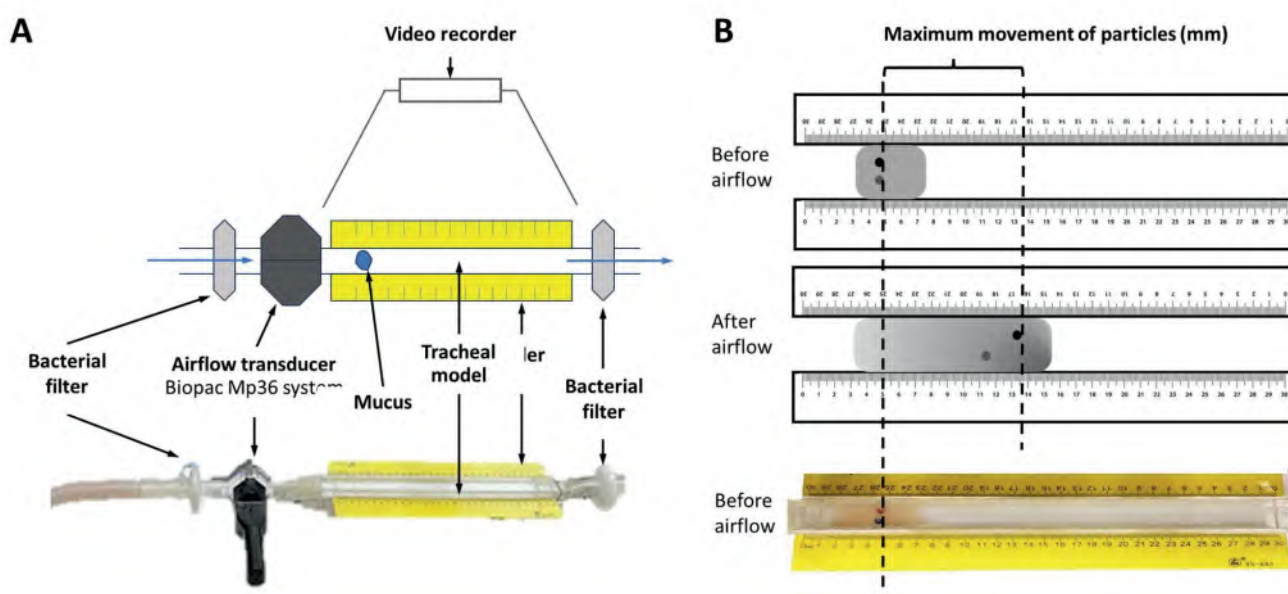


Figure 1. The cough transport setup.

A: cough transport Equipment setting, B: cough transport measurement.

Results

Table 1 presents the characteristics of the bronchiectasis patients. Ten participants collected sputum under 9 different conditions daily in a container for a total

of 90 sputum samples. However, 45 sputum samples were sufficient for testing validity, and 30 samples were sufficient for testing reliability.

Table 1. Participants' characteristics.

Characteristics	
Male/Female: N	5/5
Age: years (mean±SD)	65±10.33
BMI, kg/m ² (mean±SD)	19±3.16
Lobes affected by bronchiectasis	
≤2 lobes: N	4
>2 lobes: N	6
Amount of sputum sample	
Sputum sample for validity test: N	45
Sputum sample for reliability test: N	30

Note: data represent as mean±SD, BMI: body mass index.

Pearson correlation analysis showed $r=0.986$ ($p=0.014$) and $r=0.771$ ($p<0.001$) between mCT and sCT in MSG and sputum, respectively (Table 2 and Figure 2). The

test-retest reliability of mCT revealed ICCs of 0.997 and 0.926 in the MSG and sputum, respectively.

Table 2. Correlations between mCT and sCT in MSG and sputum samples of patients with bronchiectasis.

mCT vs. sCT	r value	p value
MSG (N=4)	0.986	0.014
Sputum (N=45)	0.771	<0.001

Notes: mCT: modified cough transport, sCT: standard airflow cough transport, MSG: mucus simulant gel.

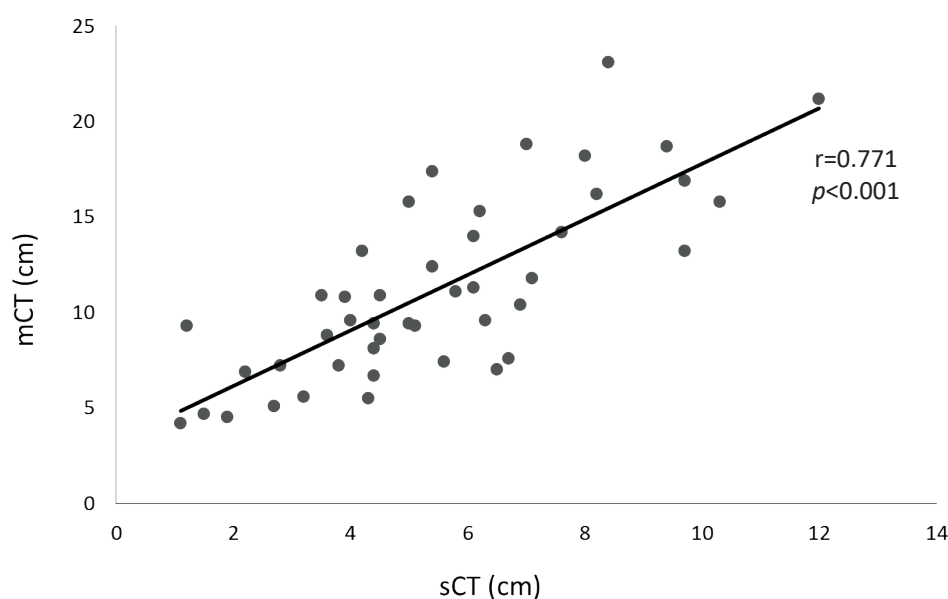


Figure 2. Scatter plot demonstrating the correlation between sCT and mCT in sputum.

Discussion

Previous studies have employed various tools to measure the viscoelasticity of respiratory secretions; among these, the magnetic rheometer is commonly accepted as the standard.^{19,20} However, this is an expensive piece of equipment to attain. Other techniques that can be used to determine viscoelasticity include measuring the wettability of mucus through contact angle measurements and measuring the spinnability of mucus using a filanometer.^{5,6,8} Both methods also require advanced technology and cannot be easily set up.

In contrast, measuring viscosity using an Ostwald viscometer is simple and cost-effective.^{21,22} However, due to its semi-solid nature, sputum cannot easily flow down the capillary of the viscometer. Therefore, this method requires vigorous stirring and dilution with water, which destroys the natural state of the mucus.²² Another inexpensive approach involves the continuous shearing method using a rotational viscometer, which has been utilized to measure sputum viscosity.^{23–26} However, this technique necessitates applying shear at different rates, making it unsatisfactory due to the shear-thinning nature of the respiratory mucus.

Cough, natural airflow dependence clearance of the body, has been influenced by the viscoelasticity of mucus. In other words, the higher the viscoelasticity of the mucus, the less cough clearance of the mucus.^{11,12} Previous studies

have used the cough transport technique as an outcome to represent changes in the viscoelasticity of mucus.^{6,8,27–30} This protocol for cough transport was mainly adapted from Agarwal *et al.* and King *et al.* as these researchers explored the nature of cough, the mucus effect on cough, the cough's impact on mucus rheology, and the function of the sol layer in clearance.^{9,10} A notable limitation of these studies is their use of higher airflow rates for cough transport, such as 5 L/s, 8 L/s, and 11 L/s, making applying this technique challenging due to difficulties in generating such high airflow. Therefore, this study aimed to explore the feasibility of modified cough transport using a slower airflow of 2 L/s.

The results of the present study showed a very high correlation ($r=0.986$, $p=0.014$) between the standard airflow of 8 L/s and the lower airflow of 2 L/s in terms of MSG. A high correlation ($r=0.771$, $p<0.001$) was also observed between sCT and mCT regarding the sputum of patients with bronchiectasis. The minor differences observed between MSG and real sputum were expected since MSG mimics sputum texture but does not replicate its chemical structure. The reliability of mCT for MSG and sputum was excellent. To the researcher's knowledge, this study was the first to determine the feasibility of using slower airflow in cough transport outcomes. Therefore, it is impossible to compare our research results with those of others.

Our study's mucus clearance technique (mCT) differed from the standard clearance technique (sCT) and airflow rate. Previous studies have used the bulk transport of mucus to determine displacement in sCT.^{8,27,28} In the current study, we determined the outcome of mCT using the maximum movement of particles that lay on mucus. Since sputum is semiliquid, using the sputum particles to measure displacement may be more accurate. However, observing displaced cough transport particles is a topic that was also researched by King M. *et al.*¹⁰

Previous studies of sCT applied very short durations concerning airflow duration, such as 100 ms,³¹ 500 ms,³⁰ and 1 s.¹⁶ We require adequate airflow to facilitate movement. Airflow rates as high as 8 L/s mimic coughing but can lead to the dispersion of mucus mist, particularly with less viscous mucus, making it challenging to measure the distance. We aim to assess whether lower, more accessible flow rates can effectively move mucus. Additionally, we are extending the duration of airflow to 6 sec to ensure sufficient movement. This approach is based on our previous unpublished research that successfully demonstrated mucus movement using these methods.³² In our study, the mCT (low airflow rate with long duration) moved longer distances than the sCT (high airflow rate with short duration) in all samples, both MSG and real sputum. Therefore, it can be said that flow rate and airflow duration play an essential role in cough transport.

The correlation between low and high airflow rates in measuring mucus viscoelasticity may be attributed to the intrinsic properties of the mucus, including its shear-thinning behavior, viscoelastic response, and duration of stress application (airflow duration). High airflow rates, such as those used in sCT, impose immediate and intense shear stress on mucus, swiftly deforming and displacing it. In contrast, low airflow rates, like those employed in mCT with a longer duration (6 sec compared to 1 sec in sCT), apply gentler but sustained shear stress. This extended exposure allows sufficient time for mucus to deform and displace, thereby establishing a correlation between the measurements taken at different airflow rates.

Our study collected sputum samples from ten patients under different conditions (pre-airway clearance session, during airway clearance session, and post-airway clearance session). Despite screening over 500 patients from the chest clinics from 3 hospitals, only 50 were diagnosed with bronchiectasis. Of these, only 10 produced sufficient daily sputum for the study. This limitation should be considered, and collecting sputum samples from more patients with bronchiectasis would be preferable. This study is the first to determine the validity of sCT and mCT. However, the calculated sample size from our result was 2 for MSG and 4 for sputum with alpha 0.05 and power 80%.¹⁷ Therefore, it was sufficient power to conclude from our results.

We are aware of the limitations of our study. The volume of mucus we used in mCT was 2 mL, which is more than some other studies used.^{8,27,28} However, this quantity of mucus was visible in the video recordings, and it enhanced the adherence of particles to the mucus during

the test. The duration of airflow also appeared longer. Future studies should address these points, refine mCT for a more feasible cough transport technique, and measure the validity with the direct viscosity measurement from the viscometer.

Conclusion

High correlations between sCT and mCT were determined in MSG and real sputum, with excellent reliability. This suggests that mCT could be an alternative to the high airflow rates in sCT. These findings have meaningful implications for researchers seeking a more accessible and cost-effective method to evaluate the effectiveness of interventions in terms of viscoelasticity.

Conflict of interest

There are no conflicts of interest in this study.

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References

- [1] Ramsey KA, Chen ACH, Radicioni G, Lourie R, Martin M, Broomfield A, *et al.* Airway mucus hyperconcentration in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med.* 2020; 201(6): 661-70. doi: 10.1164/rccm.201906-1219OC.
- [2] Rodríguez-Roisin R. The airway pathophysiology of COPD: implications for treatment. *COPD.* 2005; 2(2): 253-62. doi: 10.1081/COPD-57598.
- [3] Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. *Nat Rev Dis Primers.* 2018; 4(1): 45. doi: 10.1038/s41572-018-0042-3.
- [4] Baldry PE, Josse SE. The measurement of sputum viscosity. *Am Rev Respir Dis.* 1968; 98(3): 392-8. doi: 10.1164/arrd.1968.98.3.392.
- [5] Dasgupta B, Tomkiewicz RP, Boyd WA, Brown NE, King M. Effects of combined treatment with rhDNase and airflow oscillations on spinnability of cystic fibrosis sputum in vitro. *Pediatr Pulmonol.* 1995; 20(2): 78-82. doi: 10.1002/ppul.1950200205.
- [6] Daviskas E, Anderson SD, Jaques A, Charlton B. Inhaled mannitol improves the hydration and

- surface properties of sputum in patients with cystic fibrosis. *Chest*. 2010; 137(4): 861-8. doi: 10.1378/chest.09-2017.
- [7] Radtke T, Böni L, Bohnacker P, Maggi-Beba M, Fischer P, Kriemler S, *et al.* Acute effects of combined exercise and oscillatory positive expiratory pressure therapy on sputum properties and lung diffusing capacity in cystic fibrosis: a randomized, controlled, crossover trial. *BMC Pulm Med*. 2018; 18(1): 99. doi: 10.1186/s12890-018-0661-1.
 - [8] Rubin BK, Ramirez O, Ohar JA. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest*. 1996; 109(2): 348-52. doi: 10.1378/chest.109.2.348
 - [9] Agarwal M, King M, Rubin BK, Shukla JB. Mucus transport in a miniaturized simulated cough machine: effect of constriction and serous layer simulant. *Biorheology*. 1989; 26(6): 977-88. doi: 10.3233/bir-1989-26602.
 - [10] King M, Brock G, Lundell C. Clearance of mucus by simulated cough. *J Appl Physiol*. 1985; 58(6): 1776-82. doi: 10.1152/jappl.1985.58.6.1776.
 - [11] Chang AB. The physiology of cough. *Paediatr Respir Rev* 2006; 7(1): 2-8. doi: 10.1016/j.prrv.2005.11.009.
 - [12] McCool FD. Global physiology and pathophysiology of cough. *Chest*. 2006; 129(1 Suppl): 48S-53S. doi: 10.1378/chest.129.1_suppl.48S.
 - [13] Ragavan AJ, Evrensel CA, Krumpe P. Interactions of airflow oscillation, tracheal inclination, and mucus elasticity significantly improve simulated cough clearance. *Chest*. 2010; 137(2): 355-61. doi: 10.1378/chest.08-2096.
 - [14] Hassan AA, Evrensel CA, Krumpe PE. Clearance of viscoelastic mucus simulant with airflow in a rectangular channel, an experimental study. *Technol Health Care*. 2006; 14(1): 1-11.
 - [15] Zahm JM, King M, Duvivier C, Pierrot D, Girod S, Puchelle E. Role of simulated repetitive coughing in mucus clearance. *Eur Respir J*. 1991; 4(3): 311-5.
 - [16] Ramos EMC, Ramos D, Iyomasa DM, Moreira GL, Melegati KCT, Vanderlei LCM, *et al.* Influence that oscillating positive expiratory pressure using predetermined expiratory pressures has on the viscosity and transportability of sputum in patients with bronchiectasis. *J Bras Pneumol*. 2009; 35: 1190-7. doi: 10.1590/s1806-37132009001200005.
 - [17] Mukaka M. A guide to appropriate use of Correlation coefficient in medical research. *Malawi Med J*. 2012 Sep;24(3):69-71. doi: 23638278.
 - [18] Koo TK, Li MY. A Guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016; 15(2): 155-63. doi: 10.1016/j.jcm.2016.02.012.
 - [19] Dasgupta B, King M. Reduction in viscoelasticity in cystic fibrosis sputum in vitro using combined treatment with Nacystelyn and rhDNase. *Pediatr Pulmonol*. 1996; 22(3): 161-6. doi:10.1002/(SICI)1099-0496(199609)22:3<161: AID-PPUL4>3.0.CO;2-S.
 - [20] Santos MD, Milross MA, McKenzie DK, Alison JA. Bubble-positive expiratory pressure device and sputum clearance in bronchiectasis: A randomised cross-over study. *Physiother Res Int*. 2020; 25(3): e1836. doi:10.1002/pri.1836.
 - [21] Jones CU, Kluayhomthong S, Chaisuksant S, Khisanapant W. Breathing exercise using a new breathing device increases airway secretion clearance in mechanically ventilated patients. *Heart Lung*. 2013; 42(3): 177-82. doi: 10.1016/j.hrtlng.2012.12.009.
 - [22] Simon SW, Harmon GA. A comparison of various expectorant drugs employing a new method for determining sputum viscosity. *J Allergy*. 1961; 32: 493-500. doi: 0.1016/0021-8707(61)90003-x.
 - [23] Dippy JE, Davis SS. Rheological assessment of mucolytic agents on sputum of chronic bronchitics. *Thorax*. 1969; 24(6): 707-13. doi: 10.1136/thx.24.6.707.
 - [24] Picot R, Das I, Reid L. Pus, deoxyribonucleic acid, and sputum viscosity. *Thorax*. 1978; 33(2): 235-42. doi: 10.1136/thx.33.2.235.
 - [25] Russo P, Stigliani M, Protta L, Auriemma G, Crescenzi C, Porta A, *et al.* Gentamicin and leucine inhalable powder: what about antipseudomonal activity and permeation through cystic fibrosis mucus? *Int J Pharm*. 2013; 440(2): 250-5. doi: 10.1016/j.ijpharm.2012.05.077.
 - [26] Sheffner AL, Medler EM, Jacobs LW, Sarett HP. The in vitro reduction in viscosity of human tracheobronchial secretions by acetylcysteine. *Am Rev Respir Dis*. 1964; 90: 721-9. doi: 10.1164/arrd.1964.90.5.721.
 - [27] Bush A, Payne D, Pike S, Jenkins G, Henke MO, Rubin BK. Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. *Chest*. 2006; 129(1): 118-23. doi: 10.1378/chest.129.1.118.
 - [28] Kempainen RR, Williams CB, Hazelwood A, Rubin BK, Milla CE. Comparison of high-frequency chest wall oscillation with differing waveforms for airway clearance in cystic fibrosis. *Chest*. 2007; 132(4): 1227-32. doi: 10.1378/chest.07-1078.
 - [29] Kim JS, Okamoto K, Rubin BK. Pulmonary function is negatively correlated with sputum inflammatory markers and cough clearability in subjects with cystic fibrosis but not those with chronic bronchitis. *Chest*. 2006; 129(5): 1148-54. doi: 10.1378/chest.129.5.1148.
 - [30] Kondo CS, Macchionne M, Nakagawa NK, de Carvalho CRR, King M, Saldiva PHN, *et al.* Effects of intravenous furosemide on mucociliary transport and rheological properties of patients under mechanical ventilation. *Crit Care*. 2002; 6(1): 81-7. doi: 10.1186/cc1458.
 - [31] Rubin BK, Ramirez O, Zayas JG, Finegan B, King M. Respiratory mucus from asymptomatic smokers is better hydrated and more easily cleared by mucociliary action. *Am Rev Respir Dis*. 1992; 145(3): 545-7. doi: 10.1164/ajrccm/145.3.545.
 - [32] Kluayhomthong S. Efficacy of breathing exercise with oscillated inspiratory load and oscillated positive expiratory pressure for airway secretion clearance

and lung function in intubated patients both with and without mechanical ventilatory support [Doctor

of Philosophy Thesis in Physical Therapy]. [Thailand]: Graduate School, Khon Kaen University; 2018.

Combination of *Momordica charantia* L. with oxytetracycline enhanced antibacterial and antibiofilm activities against some multidrug-resistant bacteria

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ABSTRACT

Background: *Momordica charantia* L., the common name for bitter gourd, frequently used as a vegetable and in traditional medicine to treat wounds, peptic ulcers, parasites, and worms. Regarding of finding alternative ways to cure nosocomial infection caused by multidrug-resistant bacteria, bitter gourd in combination with some antibiotics may be a practical choice to reduce the cost of therapy and be devoid of side effects from antibiotics.

Objective: This study aimed to determine the antimicrobial, antibiofilm, and synergy effects of ethanol extract from bitter gourd in combination with conventional antibiotics, ampicillin, and oxytetracycline against some drug-resistant bacteria.

Materials and methods: The antimicrobial activity was tested by broth microdilution, and the lowest concentration that inhibits the visible growth of each microorganism was recorded as MIC. A checkerboard microdilution assay was designed to test the synergistic effect of bitter gourd extract. A crystal violet staining assay was carried out to test antibiofilm activity.

Results: The bitter gourd extracted by ethanol revealed antibacterial activity with a MIC range of 1.25-80 mg/mL. Synergistic effects of bitter gourd extract with ampicillin and oxytetracycline were effective against *P. mirabilis* and drug-resistant *P. aeruginosa* growth by FICI at 0.141 and 0.63, respectively. The results found that bitter gourd exhibited antibiofilm activities against *E. coli* ATCC 25922, drug-resistant *P. aeruginosa*, and Methicillin-Resistant *Staphylococcus aureus* (MRSA) at 2-4 hours after starting inoculum and the inhibitory efficacy values were 37.62%, 71.14%, and 69.87%, respectively.

Conclusion: The ethanol extract from bitter gourd had antibacterial effect, synergy effect when mixed with ampicillin and oxytetracycline.

Introduction

Momordica charantia L., common name as bitter gourd or bitter melon, belongs to family Cucurbitaceae. It has been found in tropical areas of Asia, the Amazon, east Africa, and the Caribbean.¹ In developing countries like Brazil, China, Cuba, India, Mexico, and Thailand, all parts of bitter gourd, such as fruits, vines, leaves, and even roots, have been frequently used as a vegetable as well as a folk medicine for the treatment of wounds, peptic ulcers, diarrhea, diabetes, measles, and hepatitis.² By clinical studies, phytochemicals such as triterpene glycosides, furpyronecucurbitane A, goyaglycoside I, and charantagenin revealed anti-hepatic fibrosis activity and anti-hepatoma activity for the treatment of hepatic fibrosis or carcinoma.^{3,4} Many biological active compounds found in bitter gourd included flavonoids, saponins, tannins,

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anthraquinones, and terpenoids revealed antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*.^{5,6} In addition, a few preliminary have been reported anticancer, antimalarial, antihelmintic, antioxidant, anti-inflammatory, and immunomodulatory activities of bitter gourd, and especially bitter gourd extract could be an inhibitor against SARS-CoV-2.^{1,2,7,8}

For centuries, the incidence of multidrug-resistant bacteria has risen and spread obviously because of antibiotic misuse and inappropriate consumption. Mainly, antibiotics are widely used to promote and prevent disease in agriculture and aquaculture. Commercial and conventional antibiotics such as tetracycline and ampicillin are unsuccessful in treating multi-drug-resistant infections.⁹ Moreover, there is a lack of funding to search for novel antibiotics to treat nosocomial infection caused by *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* of which caused a wide range of chronic infections in patients with severe burns, organ transplants, cystic fibrosis, COVID-19, AIDS, or cancer.¹⁰

Some strategies, such as using natural compounds derived from medicinal plants and combining medicinal plants with antibiotics, are alternative methods to reduce the spread of nosocomial infection caused by multidrug-resistant bacteria. Many reports have shown the mechanism and synergistic effect of natural products such as caffeic acid with tetracycline and quercetin with amoxicillin against some bacteria.¹¹ Antibacterial and antibiofilm synergy effects of medicinal plants in combination with antibiotics may prevent adherence of planktonic bacterial cells to medical devices such as catheters and cardiac valves.¹² Nevertheless, only a few researchers declared that essential oils in combination with antibiotics inhibited the biofilm formation of multidrug-resistant bacteria.¹² Additionally, reducing antibiotics used for growth promotion in agriculture, livestock farming, and aquaculture may be a great deal of dawn-resistant incidence.

Thus, this investigation aimed to determine single-use and synergistic antibacterial and antibiofilm activities of ethanol extract from bitter gourd and bitter gourd in combination with some conventional antibiotics against some multidrug-resistant and opportunistic bacteria. Likewise, increasing the effectiveness of traditional antibiotics with bitter gourd will be a model to elucidate the pharmacological action of bitter gourd for curing infectious diseases against multidrug-resistant bacteria.

Materials and methods

Bacteria strains

Bacillus cereus, *B. subtilis*, *Klebsiella pneumoniae* and *Proteus mirabilis* were isolated from clinical specimens. The standard strain of the experiment was *Escherichia coli* ATCC 25922. *A. baumannii*, resisted to aminoglycosides, β -lactam and quinolone, *P. aeruginosa* Code 1-375/04-2013, resisted to aminoglycosides, β -lactams, carbapenem, quinolone and Methicillin Resistant *Staphylococcus aureus* (MRSA) were confirmed and characterized by API 20 NE System. Also, *A. baumannii* and *P. aeruginosa* were

confirmed *MexA* and *MexB* genes by Polymerase Chain Reaction.¹³

Momordica charantia L. extract

The young leaves of bitter gourd (characterized as voucher number Buu-Cho/64-3) were collected from February to March 2022 in Chonburi province, Thailand. The fresh young leaves were dried under shade and sliced into tiny pieces. The 500 mg of ground leaves were extracted with 80% alcohol for 4 days.¹⁴ A rotary evaporator lyophilized the suspension of leaf extract. The crude bitter gourd extract with a 3.01% yield was kept in a protected light bottle at 4 C before being tested.

Minimum inhibition concentration (MIC) determination

The broth microdilution susceptibility test and lowest concentration inhibiting each microorganism's visible growth were recorded as MIC. as described by the Clinical and Laboratory Standard Institute (CLSI).¹⁵ Briefly, the 100 μ L of 80 mg/mL bitter gourd extract was diluted for serial two-fold dilution (ranging from 0.625 mg/mL to 80 mg/mL) by 100 μ L of Mueller Hinton Broth (MHB). Then, 100 μ L of 1.5×10^5 CFU/mL bacterial suspension was added to 100 L of MHB in a microtiter plate. The 96-well microtiter plate was incubated at 37°C for 18-24 h, and OD600 was measured by a microplate reader (VersaMax, U.S.A.). The 100% ddH₂O was negative control, and two antibiotics, ampicillin, and tetracycline, were positive control, and all treatments were determined in triplicate. The lowest concentration that prevented 100% viable growth of OD600 was recorded as the MIC. All MICs were determined in triplicate.

Synergistic effect determination

The checkerboard broth microdilution assay was modified to test the synergistic effect of bitter gourd extract on bacterial growth.¹⁶ The 50 μ L of two-fold serial concentrations of bitter gourd extract and 50 μ L of two-fold serial concentrations of ampicillin and oxytetracycline ranging from 1.25 mg/mL to 80 mg/mL were tested by broth microdilution susceptibility test. The triplicate sampling of synergistic MIC was analyzed. The checkerboard microdilution results of synergistic effect were compared to MICs of a single dose of bitter gourd extract and antibiotics. The fractional inhibitory of synergistic effects was calculated. FICIs were interpreted by the following: a synergism as FICI index of $FICI \leq 0.5$, a partial synergism, as FICI index of $0.5 < FICI < 1$, an additive effect, as FICI index of $FICI = 1$, an indifferent effect, as FICI index of $1 < FICI \leq 4$, an antagonism, FICI index of $FICI > 4$.¹⁶

Antibiofilm activity assay

The antibiofilm method was modified from Zheng et al. (2021).¹⁷ Briefly, 100 μ L aliquot of sample / positive control (oxytetracycline) was mixed with 100 μ L of 1×10^6 CFU/mL of bacterial culture in flat-bottomed 96-well microtiter plates, and 100 μ L of Tryptic Soy broth (TSB, Difco, U.S.A.) were applied to microplates. Next, microplates were incubated for 2-24 h. At an interval, each

well of adherent biofilm of bacteria was stained with 1% crystal violet for 15 minutes and fixed with 200 μ L of 100% methanol for 15 minutes. The stain of bacterial biofilm was solubilized by 150 μ L of 33% glacial acetic acid. Finally, the soluble biofilm of bacteria was measured in the OD600 by a microplate reader VersaMax (U.S.A.). All treatments were done in triplicate. The absorbance and percentage inhibition of biofilm of each strain were determined by triplicate sampling as equation 1.

$$\% \text{ inhibition} = (\text{OD}_{\text{control}} - \text{OD}_{\text{treatment}}) / \text{OD}_{\text{control}} \times 100 \quad (1)$$

$\text{OD}_{\text{control}}$: optical density of bacteria without compound or antibiotic.

$\text{OD}_{\text{treatment}}$: the optical density of bacteria mixed with compound.

Results

Determination MICs of bitter gourd extract

The MIC values of single-use bitter gourd extract or single use or ampicillin/oxytetracycline were summarized in Table 1. The bitter gourd extracts inhibited the growth of all bacterial strains with 80 mg/mL of MIC except for *B. cereus*. The bitter gourd extract showed the best activity against MRSA. In addition, ampicillin and tetracycline activity showed significantly better than bitter gourd extract.

Table 1. The antibacterial activity of bitter gourd extract and antibiotics against some opportunistic bacteria.

Bacteria	Minimum Inhibitory Concentration (MIC) (mg/mL)		
	<i>Momordica charantia</i>	Oxytetracycline	Ampicillin
<i>A. baumannii</i>	80	40	80
<i>B. cereus</i>	>80	20	40
<i>B. subtilis</i>	20	2.5	>80
<i>E. coli</i> ATCC 25922	80	80	80
<i>K. pneumoniae</i>	80	1.25	1.25
MRSA	1.25	20	1.25
MDR <i>P. aeruginosa</i>	80	2.5	10
<i>P. mirabilis</i>	80	20	1.25

Synergistic effect of bitter gourd extract in combination with antibiotics

The synergistic effect of the bitter gourd extract in combination with both ampicillin and oxytetracycline (Table 2) was observed against all bacteria except *A. baumannii* and *E. coli* ATCC25922. The best synergism effect

of bitter gourd in combination with tetracycline was shown against *P. mirabilis* (FICI = 0.141) and multidrug-resistant *P. aeruginosa* (FICI = 0.63). Unfortunately, synergistic effect of ampicillin or oxytetracycline mixing with bitter gourd extract against *A. baumannii*, *B. cereus*, *B. subtilis* and *E. coli* ATCC25922 was impractical (data was not shown).

Table 2. The synergistic effect of bitter gourd extract in combination with antibiotics against bacteria.

Bacteria	The synergistic effect of bitter gourd extract in combination with antibiotics			
	bitter gourd extract + Ampicillin		bitter gourd extract + Oxytetracycline	
	FICI	Interpretations	FICI	Interpretations
<i>K. pneumoniae</i>	2.016	Indifferent	2.016	Indifferent
<i>P. mirabilis</i>	-	-	0.141	Synergism
MDR <i>P. aeruginosa</i>	0.63	Partially synergism	-	-
MRSA	2	Indifferent	1.063	Indifferent

Note: - represented as no FICI. a synergism, as FIC index of ≤ 0.5 , a partial synergism, as FIC index of $0.5 < \text{FICI} < 1$, an additive effect, as FICI index of $\text{FICI} = 1$, an indifferent effect, as FICI index of $1 < \text{FICI} \leq 4$, an antagonism, FICI index of $\text{FICI} > 4$

Antibiofilm activity of bitter gourd extract

The inhibitive effect of biofilm formation of *E. coli* ATCC 25922, MRSA, and drug-resistant *P. aeruginosa* was shown in Figure 1-3, and at the concentration of 80 mg/mL, a single dose of bitter gourd extract indicated significant antibiofilm activity against all tested strains at 2-4 h and % inhibition ranging from 37.14%-71.14%

($p < 0.05$). A combination of 80 mg/mL bitter gourd extract and 80 mg/mL oxytetracycline showed significantly better antibiofilm activity than a single dose of bitter gourd extract or oxytetracycline at 2-8 h against MRSA and multidrug-resistant *P. aeruginosa*. However, bitter gourd extracts alone or combined with ampicillin showed no effect (data not shown).

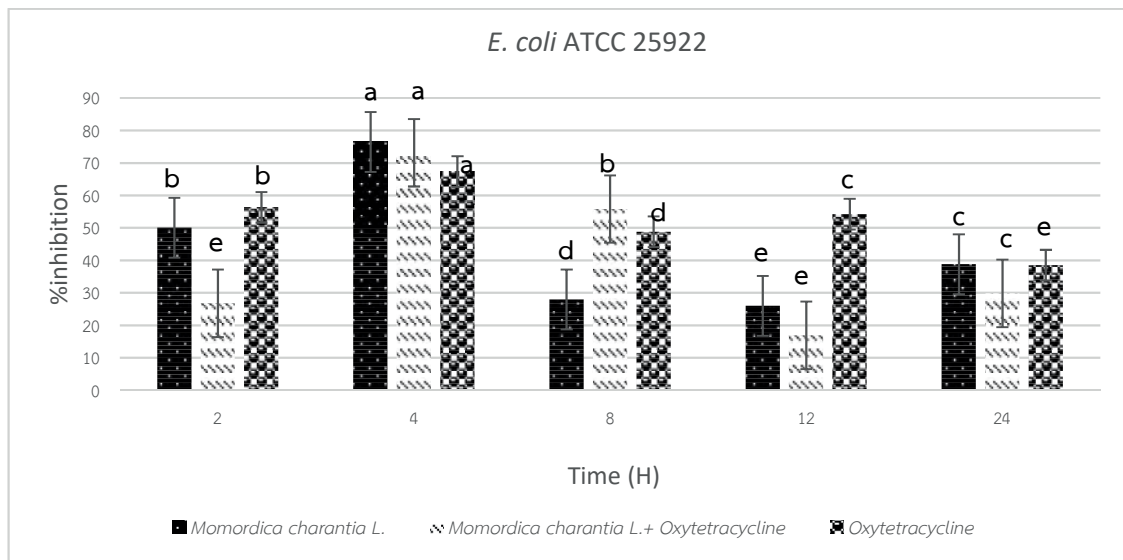


Figure 1. Effect of 80 mg/mL bitter gourd extract in combination with 80 mg/mL oxytetracycline on biofilm formation of *E. coli* ATCC 25922. * $a-e$ significant different ($p \leq 0.05$).

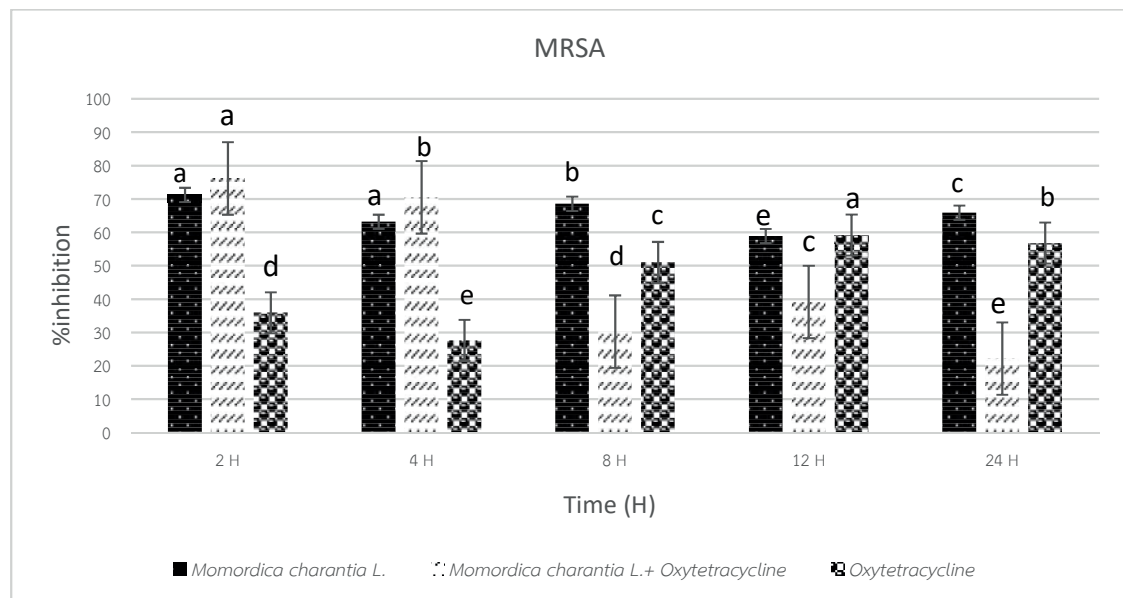


Figure 2. Effect of 80 mg/mL bitter gourd extract in combination with 80 mg/mL oxytetracycline on biofilm formation of MRSA. * $a-e$ significant different ($p \leq 0.05$).

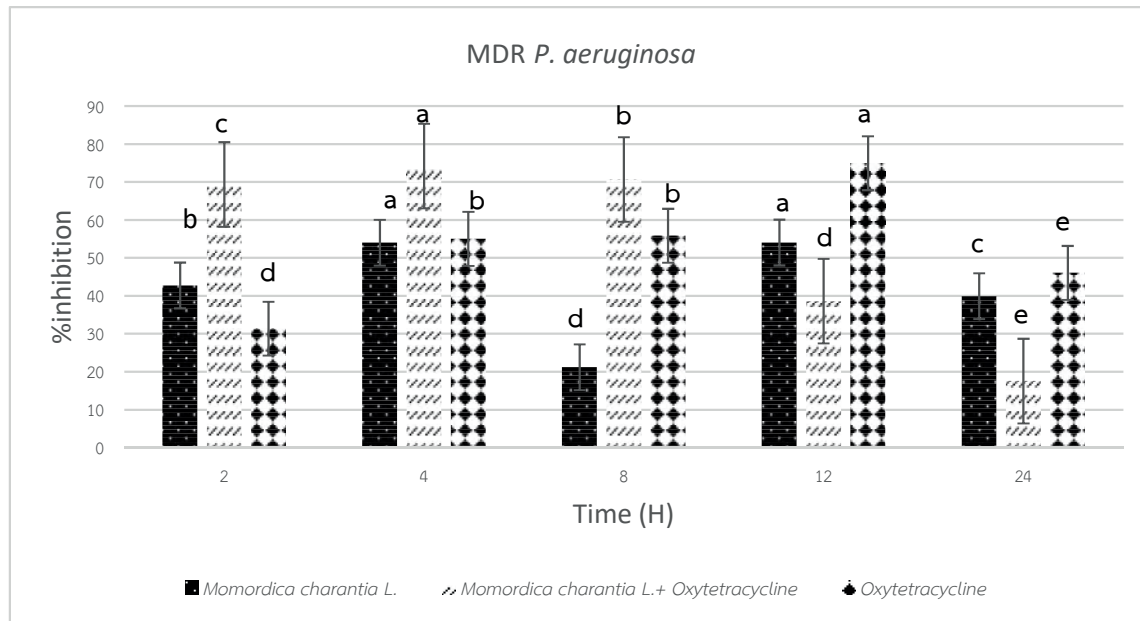


Figure 3. Effect of 80 mg/mL bitter gourd extract in combination with 80 mg/mL oxytetracycline on biofilm formation of multidrug resistant *P. Aeruginosa*. *^{a-e}different superscript letter within Each bar are represented significantly different ($p \leq 0.05$).

Discussion

Multidrug-resistance causes severe problems and impacts the treatment of infectious diseases. Accumulation of opportunistic bacteria, including *A. baumannii*, *E. coli*, *K. pneumoniae*, MRSA, and *P. aeruginosa*, caused by innate genetics and physiological transmission.⁹ It was the most troublesome problem in pharmacological industries and clinical treatment of infected patients that standard antibiotics, ampicillin, and oxytetracycline right now were inactive and could not be helpful to treat infected patients.¹⁰ The bitter gourd may solve the problem of how to bring conventional antibiotics back to treat bacterial coinfection with COVID-19 and to reduce the side effect of these antibiotics.⁷ In this research, bitter gourd extracted showed a well-known antibacterial activity against some multidrug-resistant bacteria due to many secondary metabolites, such as tannins, flavonoids, and alkaloids, which had many biological actions.¹⁸ In some reports, the antibacterial result declared that ethanol extract of bitter gourd showed only antibacterial activity against *S. aureus* when using MIC as 1.25 $\mu\text{g/mL}$ as the same result, this study showed antibacterial effect against MRSA (MICs of 1.25 mg/mL).¹⁹

The synergistic effect of this report indicated that bitter gourd extract in combination with both ampicillin and oxytetracycline exhibited the highest efficiency against *P. mirabilis* and drug-resistant *P. aeruginosa*. As the result of Wagner and Ulrich-Merzenich, the synergistic effect of bitter gourd extract may improve solubility, reabsorption rate of ampicillin and tetracycline and inhibit proteins such as enzyme and transport protein, ribosome, DNA, and RNA synthesis of gram-negative bacteria.²⁰ Bitter gourd extract contains phenolic compounds like the essential oil of *Thymus vulgarism*, such as p-cymene, γ -terpinene, and thymol so that bitter gourd extract could

inhibit the growth of *E. coli*, *K. pneumoniae*, and *S. aureus*.²¹ In particular, Mallotojaponin B, in combination with chloramphenicol, showed the same synergistic effect with FICI 0.393 against MRSA and indicated the mechanism that caused alteration and destruction of the cell membrane of MRSA.²² In addition, this was consistent with the finding of Navy et al. that oxytetracycline in combination with epigallocatechin gallate (EGCG) could inhibit the growth of *S. aureus*.²³ Likely, Vipin et al. found that quercetin with levofloxacin, ceftriaxone, gentamycin, tobramycin, and amikacin showed 68 to 85% reducing the growth of multidrug-resistant *P. aeruginosa*.

The initial stage of biofilm formation was a target goal to inhibit bacterial growth and adhere to their target surface. In this study, results indicated that bitter gourd extract in combination with oxytetracycline showed potential antibiofilm activity against all bacterial strains. Based on our findings on the antibiofilm activity of drug-resistant bacteria, the highest dose of bitter gourd extract and oxytetracycline showed a synergistic effect with MIC (80 mg/mL). Based on the study, the lowest MIC values of 25 $\mu\text{g/mL}$ and 250 $\mu\text{g/mL}$ of the inhibitory effect of grape seed fruit were used. This study showed better activity than the antibiofilm activity of bitter gourd against *S. aureus* and *E. coli*.²⁴ Moreover, Vipin et al. studied the synergistic activity of quercetin at 125 $\mu\text{g/mL}$ and showed a synergistic effect with $\frac{1}{2} \times \text{MIC}$ or $\frac{1}{4} \times \text{MIC}$ of levofloxacin (125 $\mu\text{g/mL}$) against *P. aeruginosa*.²⁵ Thus, bitter gourd extracts enhanced antibiofilm activity of oxytetracycline against *E. coli*, MRSA, and *P. aeruginosa* may be closely related to actions of flavonoids, saponins, tannins, anthraquinones as the primary component found in bitter gourd leave.^{6,26}

This study showed a successful report that bitter gourd extract could synergize the antibacterial activity

of ampicillin and oxytetracycline to inhibit opportunistic and drug-resistant bacteria growth. Also, the success of bitter gourd extract in combination with oxytetracycline may be helpful to prevent some drug-resistant bacterial growth and biofilm formation. Thus, bitter gourd may be a choice for the therapeutic management of nosocomial infection. However, no mechanism has been explained for the antimicrobial activity of bitter gourd extract. Toxicity and interaction of bitter gourd with oxytetracycline may be tested in the future.

Conclusion

In this study, young leaves of bitter gourd extract can synergize oxytetracycline's antibacterial and antibiofilm activities to inhibit the growth of some opportunistic and drug-resistant bacteria, such as *E. coli*, MRSA, and *P. aeruginosa*. A combination of antibiotics and bitter gourd may be a choice for therapeutic management of caring for infectious diseases and reducing the overuse of antibiotics in environments.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Jia S, Shen M, Zhang F, Xie J. Recent Advances in *Momordica charantia*: Functional Components and Biological Activities. *Int J Mol Sci*. 2017; 18(12): 2555. doi: 10.3390/ijms18122555.
- [2] Saeed, F, Afzaal, M, Niaz, B, Arshad, MU, Tufail, T, Hussain, MB, et al. Bitter melon (*Momordica charantia*): a natural healthy vegetable. *Int. J. Food Prop*. 2018; 21(1): 1270-90. doi: 10.1080/10942912.2018.1446023.
- [3] Deng Y, Tang Q, Zhang Y, Zhang R, Wei Z, Tang X, et al. Protective effect of *Momordica charantia* water extract against liver injury in restraint-stressed mice and the underlying mechanism. *Food Nutr. Res*. 2017; 61(1): 1348864. doi: 10.1080/16546628.2017.1348864.
- [4] Yue J, Sun Y, Xu J, Cao J, Chen G, Zhang H, et al. Cucurbitane triterpenoids from the fruit of *Momordica charantia* L. and their anti-hepatic fibrosis and anti-hepatoma activities. *Phytochem*. 2019; 157: 21-7. doi: 10.1016/j.phytochem.2018.10.009.
- [5] Jagessar RC, Mohamed A, Gomes G. An evaluation of the antibacterial and antifungal activity of leaf extracts of *Momordica charantia* against *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli*. *Nat. Sci*. 2008; 6(1): 1-14.
- [6] Ingle A, Kapgate R. Phytochemical screening and anti-microbial activity of *Momordica charantia* Linn. *Int. J. Pharm. Res*. 2018; 8(7): 63-5. doi: 10.74: 39/ijpr.
- [7] Evary YM, Masyita A, Kurnianto AA, Asri RM, Rifai Y. Molecular Docking of Phytochemical Compounds of *Momordica charantia* as Potential Inhibitors against SARS-CoV-2. *Infect. Disord. Drug Targets*. [serial online]. 2022; 22(3): e130122200221. doi: 10.2174/1871526522666220113143358.
- [8] Gayathry, KS, John, JA. A comprehensive review on bitter gourd (*Momordica charantia* L.) as a gold mine of functional bioactive components for therapeutic foods. *Food Prod. Process. Nutr*. 2022; 4(1): 1-14. doi: 10.1186/s43014-022-00089-x.
- [9] Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018; 24(3): 482-501. doi: 10.3934/microbiol.2018.3.482.
- [10] Cheesman MJ, Ilanko A, Blonk B, Cock IE. Developing new antimicrobial therapies: are synergistic combinations of plant extracts/compounds with conventional antibiotics the solution? *Phcog Rev*. 2017; 11(22): 57-72. doi: 10.4103/phrev.phrev_21_17.
- [11] Álvarez-Martínez FJ, Barrajón-Catalán E, Herranz-López M, Micol V. Antibacterial plant compounds, extracts and essential oils: An updated review on their effects and putative mechanisms of action. *Phytomedicine*. [serial online]. 2021; 90: 153626. doi: 10.1016/j.phymed.2021.153626.
- [12] Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi K.R. Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: A review. *Front. Microbiol*. 2019; 10: 539. doi: 10.3389/fmicb.2019.00539.
- [13] Nehme D, Li XZ, Elliot R, Poole K. Assembly of the MexAB-OprM multidrug efflux system of *Pseudomonas aeruginosa*: identification and characterization of mutations in *mexA* compromising MexA multimerization and interaction with MexB. *J. Bacteriol*. 2004; 186(10): 2973-83. doi: 10.1128/jb.186.10.2973-2983.2004.
- [14] Tan SP, Parks SE, Stathopoulos CE, Roach PD. Extraction of flavonoids from bitter melon. *Food and Nutrition Sciences*. 2014; 5(5): 458-65. doi: 10.4236/fns.2014.55054.
- [15] CLSI. Performance standards for antimicrobial susceptibility testing. 27th Ed., Suppl. M100. Wayne, PA, Clinical and Laboratory Standards Institute; 2017.
- [16] Hall MJ, Middleton RF, Westmacott D. The fractional inhibitory concentration (Fic) index as a measure of synergy. *J. Antimicrob. Chemother*. 1983; 11: 427-33. doi: 10.1093/jac/11.5.427.
- [17] Zheng X, Chen L, Zeng W, Liao W, Wang Z, Tian X, et al. Antibacterial and anti-biofilm efficacy of chinese dragon's blood against *Staphylococcus aureus* isolated from infected wounds. *Front. microbiol*. 2021; 12: 672943. doi: 10.3389/fmicb.2021.672943.

- [18] Torre VE, Guarniz WS, Silva-Correa C, Cruzado-Razco L, Raúl Siche R. Antimicrobial Activity and Chemical Composition of *Momordica Charantia*: A Review. *Pharmacog J.* 2020; 12: (1)213-22. doi: 10.5530/pj.2020.12.32
- [19] Guarniz W, Canuto K, Ribeiro P, Dodou H, Magalhaes K, Sa K. *Momordica Charantia* L. variety from Northeastern Brazil: Analysis of Antimicrobial Activity and Phytochemical Components. *Pharmacog J.* 2019; 11(6):1312-24. doi: 10.5530/pj.2019.11.203.
- [20] Wagner H, Ulrich-Merzenich G. Synergy research: Approaching a new generation of Phytopharmaceuticals. *Phytomedicine.* 2009; 16: 97-110. doi: 10.1016/j.phymed.2008.12.018.
- [21] Al-Bayati, FA. Synergistic antibacterial activity between *Thymus vulgaris* and *Pimpinella anisum* essential oils and methanol extracts. *J. Ethnopharmacol.* 2008; 116: 403-6. doi: 10.1016/j.jep.2007.12.003.
- [22] Bonincontro G, Scuderi SA, Marino A, Simonetti G. Synergistic effect of plant compounds in combination with conventional antimicrobials against biofilm of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida* spp. *Pharmaceuticals.* 2023; 16(11): 1531. doi: 10.3390/ph1611153.
- [23] Novy P, Rondevaldova J, Kourimska L, Kokoska L. Synergistic interactions of epigallocatechin gallate and oxytetracycline against various drug resistant *Staphylococcus aureus* strains in vitro. *Phytomedicine.* 2013; 20(5): 432-5. doi: 10.1016/j.phymed.2012.12.010.
- [24] Song YJ, Yu HH, Kim YJ, Lee NK, Paik HD. Anti-biofilm activity of grapefruit seed extract against *Staphylococcus aureus* and *Escherichia coli*. *L. Microbial. Biotechnol.* 2019; 29(8): 1177-83. doi: 10.1041/jmb.1905.05022.
- [25] Vipin M, Mujeeburahiman K, Saptami, AB, Arun PD, Rekha PD. Synergistic interactions of quercetin with antibiotics against biofilm associated clinical isolates of *Pseudomonas aeruginosa* in vitro *BioRxiv.* [Internet]. 2019; Available from: <https://doi.org/10.1101/601336>.
- [26] Chokki M, Cheikna Z, Dah-Nouvlessounon D, Baba-Moussa F. (2020). Phytochemical screening and antimicrobial activity of *Momordica charantia* L. and *Morinda lucida* Benth extracts from Benin. *Afr. J. Microbiol. Res.* 2020; 14(8): 426-35. doi: 10.5897/AJMR2020.9347.

Preliminary study: Exploring the influence of healthcare services and antibiotic discontinuation among pulmonary tuberculosis patients with self-administration in Western Thailand: A case-control study

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ABSTRACT

Background: Outpatients generally use self-administration, which might result in defaulting from treatment.

Objective: This study evaluated the association between patient treatment discontinuation and health service.

Materials and methods: This retrospective case-control study was conducted in a TB clinic at Makarak Hospital, Kanchanaburi Province, Thailand. Participants who completed and discontinued treatment from 2017 to 2021 were surveyed using questionnaires.

Results: A total of 198 patients with TB who discontinued (N=49) and completed treatment (N=149) were analyzed. Associated factors of discontinued treatment in those who were male were (OR=8.41, 95%CI: 1.55-45.61), not receiving support from a family member (OR=33.75, 95%CI: 3.22-353.76), and waiting time of more than 3 hours for health services (OR=9.39, 95%CI: 1.98-44.64).

Conclusion: Prolong treatment delivery services that exceed more than 3 hours and living without family support were associated with drug discontinuation in patients with TB who were self-administration treatment. These factors should be considered to enhance TB treatment success and infection control.

Introduction

Pulmonary tuberculosis (PTB) remains a significant public health concern with global implications.^{1,2} The Global Tuberculosis 2023 report reported that the incidence rate of new and relapsed TB cases was estimated at approximately 150 per 100,000 people, particularly in western Thailand.^{4,5}

Antibiotics (ATB) is the standard treatment for TB infection. The estimated TB treatment coverage among Thai people is 67%.³ Medication adherence is crucial for treatment successiveness. Inappropriate adherence, especially treatment discontinuation, is the possibility of developing antibiotic-drug resistance, which results in the persistence of the infection, enhanced transmission, and high relapse rates and becomes more complex, costly, and less successful due to these strains' resistance to the medications.^{6,7}

Directly observed treatment short (DOTs) course is recommended for TB treatment. This strategy is for encouraging patients to receive medication adequately and results in increased treatment progression and

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infection control.⁸ Self-administration treatment (SAT) is uncommonly used, and some patients are at risk of self-adjusted doses of medication, which results in defaulting to TB treatment. However, previous systematic reviews and meta-analyses showed DOTs were not superior to SAT.^{9,10}

One of the main challenges of TB control is avoiding the acquisition of drug resistance. However, directly observed treatments are limited in some areas; thus, outpatients generally use SAT, and healthcare delivery systems are reasonable to apply. However, the risk of discontinuation of TB treatment has remained. Therefore, drug discontinuation in outpatients who have self-administration and collaborate with healthcare services in local Thai areas is not well established. This study explored the factors that affected drug discontinuation, particularly in healthcare services.^{6,8,11-15}

Materials and methods

Study design and participants

A retrospective case-control study was conducted among TB patients who tested IGRA positive and aged over 15 years old were included in this study. All participants were self-administered during the continuation phase of TB treatment, during which the healthcare providers instructed the medication procedure participants. Those who discontinued treatment by interviewing were assigned to the study group, whereas those who always continued TB treatment were assigned to the control group. Informed consent was obtained before participating in this study. This study was approved by the Institutional Review Board of Makarak Hospital (IRB number 2/65).

Protocol

Participants were registered at the TB clinic, and data were collected from the pulmonary TB clinic at Makarak Hospital from 2017 to 2021. The questionnaire was developed based on a review of literature related to factors associated with treatment discontinuation in pulmonary TB patients. It was pre-tested and revised with

feedback from a focus group of nurses and staff members responsible for identifying case controls and recording participant information at the TB clinic. Three experts evaluated the content validity of the research tool before it was used in the study. The questionnaire collected information on sociodemographic factors, such as sex, age, marital status, religion, ethnicity, educational level, occupation, household members, and family support, as well as details about travel time to the hospital and waiting time for services at the TB clinic.

Data analysis

For the descriptive analysis, frequencies and percentages were used for categorical data, whereas means and standard deviations were used for continuous data. Chi-squared tests were used to determine the factors associated with discontinuation. The level of significance was set at $p < 0.05$.

A conditional logistic regression model included all variables with a $p < 0.20$ in univariate analysis. Binary logistic regression was used to analyze factors related to treatment discontinuation in patients with PTB.

Results

A total of 198 patients with PTB were eligible for participation in the study. The majority were aged 46-60 (34.80%), men (67.70%), Buddhists (98.00%), and Thais (98.00%).

The characteristics of the participants in the study and control groups and the factors associated with the discontinuation of TB treatment in the univariate analysis (Table 1). Significant factors for discontinuing TB treatment included being male, unmarried, Buddhist, Furthermore, having primary education, being employed, living with household members, not receiving support from family members, biking to the hospital, and having a waiting time of more than 3 hours for services at the TB clinic were additional significant factors related to treatment discontinuation ($p < 0.05$).

Table 1. Sociodemographic factors associated with discontinuing tuberculosis treatment among the study and control groups.

Factor	Total participants (N=198)		Chi-square	p value
	Discontinuation (N=49)	Control (N=149)		
Gender			4.226	0.040
Male	39 (19.70)	95 (47.98)		
Female	10 (5.05)	54 (27.27)		
Age (years)			4.593	0.332
15-30	9 (4.55)	13 (6.57)		
31-45	9 (4.55)	28 (14.14)		
46-60	18 (9.09)	51 (25.76)		
61-75	9 (4.55)	40 (20.20)		
>76	4 (2.02)	17 (8.59)		

Table 1. Sociodemographic factors associated with discontinuing tuberculosis treatment among the study and control groups (continued).

Factor	Total participants (N=198)		Chi-square	p value
	Discontinuation (N=49)	Control (N=149)		
Type of TB			5.012	0.171
TB	34 (17.2)	122 (61.6)		
MDR-TB	12 (6.1)	21 (10.6)		
Pre-XDR-TB	3 (1.5)	4 (2.0)		
XDR-TB	0 (0.0)	2 (2.10)		
Comorbidity			6.102	0.014
Yes	17 (8.6)	82 (41.4)		
No	32 (16.2)	67 (33.8)		
Drug side effect			2.748	0.097
Yes	41 (20.7)	107 (54.0)		
No	8 (4.0)	42 (23.7)		
Marital status			17.485	<0.001
Single	21 (10.61)	24 (12.12)		
Married	17 (8.59)	96 (48.48)		
Widowed/separated	11 (5.56)	29 (14.65)		
Religion			12.414	<0.001
Buddhist	45 (22.73)	149 (75.25)		
Others	4 (2.02)	0 (0.00)		
Ethnicity			12.414	<0.001
Thai	45 (22.73)	149 (75.25)		
Not Thai	4 (2.02)	0 (0.00)		
Level of education			17.186	0.004
Non-formal	8 (4.04)	7 (3.54)		
Primary	26 (13.13)	90 (45.45)		
Secondary	15 (7.58)	28 (14.14)		
Diploma, vocational certificate	0 (0.00)	10 (5.05)		
Undergraduate	0 (0.00)	13 (6.57)		
Postgraduate	0 (0.00)	1 (0.51)		
Occupation			23.448	<0.001
Agriculture	3 (1.52)	22 (11.11)		
Employment	37 (18.69)	54 (27.27)		
Government service	0 (0.00)	7 (3.54)		
Business owner	2 (1.01)	12 (6.06)		
Others	7 (3.54)	54 (27.27)		
Number of household members			28.270	<0.001
1-2	30 (15.15)	31 (15.66)		
3-5	16 (8.08)	98 (49.49)		
>5	3 (1.52)	20 (10.10)		
Receiving support from a family member			62.673	<0.001
Yes	22 (11.11)	141 (71.21)		
No	27 (13.64)	8 (4.04)		
Method used for travel to the hospital			29.765	<0.001
Walking	2 (1.01)	0 (0.00)		
Bicycling	0 (0.00)	1 (0.51)		
Motorbike	29 (14.6)	75 (37.88)		
Car	11 (5.56)	72 (36.36)		
Bus	7 (3.54)	1 (0.51)		

Table 1. Sociodemographic factors associated with discontinuing tuberculosis treatment among the study and control groups (continued).

Factor	Total participants (N=198)		Chi-square	p value
	Discontinuation (N=49)	Control (N=149)		
Distance from home to the hospital (km)			2.219	0.528
<5	4 (2.02)	23 (11.62)		
5-15	36 (18.18)	94 (47.47)		
16-30	8 (4.04)	28 (14.14)		
>31	1 (0.51)	4 (2.02)		
Waiting time for services at the TB clinic (hour)			23.824	<0.001
<1	1 (0.51)	2 (1.01)		
1-2	8 (4.04)	84 (42.42)		
>3	40 (20.20)	63 (31.82)		

Note: data represented as N (percentage).

The factors related to treatment discontinuation in patients with PTB from the final regression model using binary logistic regression are shown in Table 2. Significant factors for discontinuing TB treatment were male sex

(OR=8.41; 95% CI=1.55-45.61), living without support from a family member (OR=33.75; 95% CI=3.22-353.76), and a waiting time of more than 3 hours at the TB clinic to receive treatment (OR=9.39; 95% CI=1.98-44.64).

Table 2. Factors related to the discontinuation of treatment in patients with pulmonary tuberculosis.

Variable	B	SE	Wald	p value	Odds ratio	95% CI	
						Lower	Upper
Sex							
Male	2.13	0.86	6.09	0.014*	8.41	1.55	45.61
Social factors							
Not receiving support from a family member	3.52	1.20	8.62	0.003**	33.75	3.22	353.76
Hospital service							
Waiting time of more than 3 hours for services at the clinic	2.24	0.80	7.93	0.005**	9.39	1.98	44.64

R-square = 0.587

* $p < 0.05$; ** $p < 0.01$

Discussion

Over the past decade, Kanchanaburi province has faced a TB epidemic in Thailand, with Tha Maka district reporting the highest rates of TB and MDR-TB infection.^{16,17} This study identified factors related to drug discontinuation in patients with pulmonary TB, focusing mainly on the influence of healthcare services. The tuberculosis clinic handles screening for both TB and MDR-TB patients and provides guidance on medication adherence to ensure that patients complete their treatment. The study found that medication-related complications were rare and were generally managed effectively by clinic staff, preventing these issues from leading to discontinuation. Additionally, evaluations revealed that the percentage of TB and MDR-TB patients remains high, as the study site is one of the largest sources of MDR-TB cases in Thailand, continuing to see new cases despite existing control measures. This situation highlights the importance of the study and is a key reason why the research focused on this issue.

This study demonstrated that male participants were more likely to discontinue treatment than female

participants (OR=8.41, 95% CI:1.55-45.61), consistent with the study by Herreo-¹⁸ which reported that men were more likely to discontinue TB therapy, with odds ratio of 2.8 (95% CI = 1.2-6.7). Additionally, Umo *et al.*¹⁹ reported that men had an odds ratio of 1.9 (95% CI = 1.2-3.0).

According to the social factor, it was the meaningful factor in patient adherence (OR=33.75, 95% CI: 3.22-353.76). The study indicated that a lack of family support to supervise and remind patients about taking their medication significantly increased the likelihood of tuberculosis patients missing doses. Therefore, patients who do not receive care from their relatives are at a higher risk of experiencing interruptions in their tuberculosis treatment, leading to less effective outcomes compared to those with family support. In contrast, Tian *et al.*⁹ reported no significant difference between family and non-family directly observed treatment. This different finding might be from socio-cultural influences.

Waiting more than 3 hours at the TB clinic was significantly associated with a higher probability of discontinuing TB treatment (OR=9.39; 95%CI: 1.98-44.64).

This finding, related to a previous study by Zegeye *et al.*,¹² revealed that waiting an hour for treatment significantly increased the chance of terminating treatment (OR=4.88; 95% CI:3.44-6.91). In addition, Muture *et al.* reported that waiting more than 1 hour at the TB clinic significantly contributed to treatment discontinuation (OR=2.34, 95CI: 1.32-4.16).⁶ Hence, these studies' results support the findings that longer waiting times at TB clinics and discontinuation of ongoing TB treatment correlate across various countries.²⁰⁻²² Waiting for healthcare service for a longer time results in negative patient satisfaction, which might increase the discontinuation treatment rate. According to the participants' characteristics, most of the occupations in this study were employers, and waiting too long might disrupt patients' income.

Therefore, pulmonary TB patients with self-administration might be drug discontinuation due to family support and waiting time of more than 3 hours since these strains are resistant to the drugs, cause the infection to persist, increase in transmission, and have a high recurrence rate.

Limitation

This study was a preliminary study with a small sample size and different proportions between groups. According to the study, it was clinical research, and participants were selected based on the patients' treatment outcomes.

Conclusion

Waiting times exceedingly more than 3 hours for receiving treatment from healthcare services and living without family support result in treatment discontinuation. Therefore, the appropriate healthcare service should be concerned with enhancing treatment success and infection control in pulmonary TB with self-administration.

Conflict of interest

There were no conflicts of interest in this study.

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References

- [1] Salame FM, Ferreira MD, Belo MT, Teixeira EG, Cordeiro-Santos M, Ximenes RA, *et al.* Knowledge about tuberculosis transmission and prevention and perceptions of health service utilization among index cases and contacts in Brazil: Understanding losses in the latent tuberculosis cascade of care. Hasnain SE, editor. PLoS ONE. 2017; 12(9): e0184061. doi.org/10.1371/journal.pone.0184061.
- [2] WHO. Global tuberculosis report 2022 [Internet]. Geneva; 2022 [cited 2023 Oct 15]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>.
- [3] WHO. Global Tuberculosis Report 2023 [Internet]. 2023 [cited 2024 May 31]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023>.
- [4] Jiraphongsa C, Wangteeraprasert T, Henpraserttae N, Sanguanwongse N, Panya L, Sukkasitvanichkul J, *et al.* Community outbreak of multidrug resistance tuberculosis, Kanchanaburi province, Thailand on 2002-June 2010. J Prev Med Assoc Thai. 2011; 1: 261-71.
- [5] Sujariyakul A, Rudeeaneksin J, Tipkrua N, Phetsuksiri B. Epidemiology and genotypes of Mycobacterium tuberculosis at an outbreak area in Kanchanaburi province. Dis Control J. 2016; 42(4): 337-47. doi.org/10.14456/dcj.2016.7.
- [6] Muture BN, Keraka MN, Kimuu PK, Kabiru EW, Ombeka VO, Oguya F. Factors associated with default from treatment among tuberculosis patients in nairobi province, Kenya: A case control study. BMC Public Health. 2011; 11(1): 696. doi.org/10.1186/1471-2458-11-696.
- [7] Garrido M da S, Penna ML, Perez-Porcuna TM, Souza AB de, Marreiro L da S, Albuquerque BC, *et al.* Factors Associated with Tuberculosis Treatment Default in an Endemic Area of the Brazilian Amazon: A Case Control-Study. PLOS ONE. 2012; 7(6): e39134. doi.org/10.1371/journal.pone.0039134.
- [8] WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva; 2022.
- [9] Tian JH, Lu ZX, Bachmann MO, Song FJ. Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies. Int J Tuberc Lung Dis. 2014; 18(9): 1092-8. doi.org/ 10.5588/ijtld.13.0867.
- [10] Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis. 2013; 57(1): 21-31. doi.org/ 10.1093/cid/cit167.
- [11] Namukwaya E, Nakwagala F, Mulekya F, Mayanja-Kizza H, Mugerwa R. Predictors of treatment failure among pulmonary tuberculosis patients in Mulago hospital, Uganda. Afr Health Sci. 2011; 11(Suppl 1): S105-11. doi.org/ 10.4314/ahs.v11i3.70079.
- [12] Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, *et al.* Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLOS ONE. 2019; 14(1): e0210422. doi.org/ 10.1371/journal.pone.0210422.
- [13] Dodor EA, Afenyadu GY. Factors associated with tuberculosis treatment default and completion at the Effia-Nkwanta Regional Hospital in Ghana. Trans

- R Soc Trop Med Hyg. 2005; 99(11): 827-32. doi.org/10.1016/j.trstmh.2005.06.011.
- [14] Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and associated factors among TB patients attending at Gondar town health centers, Northwest Ethiopia. BMC Research Notes. 2018; 11(1): 691. doi.org/10.1186/s13104-018-3789-4.
- [15] Gugssa Boru C, Shimels T, Bilal AI. Factors contributing to non-adherence with treatment among TB patients in Sodo Woreda, Gurage Zone, Southern Ethiopia: A qualitative study. Infect Public Health. 2017; 10(5): 527-33. doi.org/10.1016/j.jiph.2016.11.018.
- [16] Jiraphongsa C, Wangteeraprasert T, Henpraserttae N, Sanguanwongse N, Panya L, Sukkasitvanichkul J, *et al.* Community outbreak of multidrug resistance tuberculosis, Kanchanaburi province, Thailand on 2002-June 2010. J Prev Med Assoc Thail. 2011; 1: 261-71.
- [17] Sujariyakul A, Rudeeaneksins J, Tipkruea N, Phetsuksiri B. Epidemiology and genotypes of Mycobacterium tuberculosis at an outbreak area in Kanchanaburi province. Dis Control J. 2016 ; 42(4): 337-47.
- [18] Herrero MB, Ramos S, Arrossi S. Determinants of non adherence to tuberculosis treatment in Argentina: barriers related to access to treatment. Rev bras epidemiol. 2015; 18: 287-98. doi.org/10.1590/1980-5497201500020001.
- [19] Umo I, Kulai M, Commons RJ. Factors associated with loss to follow-up among TB patients in rural Papua New Guinea. Public Health Action. 2021; 11(4): 186-90. doi.org/10.5588/pha.21.0054.
- [20] Slama K, Tachfouti N, Obtel M, Nejari C. Factors associated with treatment default by tuberculosis patients in Fez, Morocco. East Mediterr Health J. 2013; 19(08): 687-93.
- [21] Suliman Q, Lim PY, Md. Said S, Tan KA, Mohd. Zulkefli NA. Risk factors for early TB treatment interruption among newly diagnosed patients in Malaysia. Sci Rep. 2022; 12(1): 745. doi.org/10.1038/s41598-021-04742-2.
- [22] Gube AA, Debalkie M, Seid K, Bisete K, Mengesha A, Zeynu A, *et al.* Assessment of Anti-TB Drug Nonadherence and Associated Factors among TB Patients Attending TB Clinics in Arba Minch Governmental Health Institutions, Southern Ethiopia. Tuberc Res Treat. 2018; 2018: e3705812. doi.org/10.1155/2018/3705812.

Motivational factors influencing research completion: A literature review for occupational therapy and health professions

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ABSTRACT

Background: Graduate education, particularly at the master's and doctoral levels, is crucial in developing advanced professional skills and fostering a research-oriented mindset. However, many students struggle to complete their research due to various motivational and institutional challenges. This literature review examines the factors influencing research completion in graduate school to provide insights into occupational therapy and related health professions, emphasizing the importance of intrinsic and extrinsic motivational factors.

Objective: The primary goals of this review are to (1) identify the intrinsic and extrinsic motivational factors that influence research completion, (2) explore the barriers to research completion at the graduate level, and (3) propose motivational strategies that graduate programs can adopt to support research completion among occupational therapy and other health professions.

Materials and methods: A literature search was conducted across multiple databases, including the ASEAN Citation Index, EBSCO, Google Scholar, and Scopus. The review focused on studies published between 2010 and 2024 investigating motivational strategies, barriers, and research completion in graduate school. A total of 17 peer-reviewed articles met the inclusion criteria and were subjected to frequency and thematic analyses to identify key themes and patterns.

Results: The thematic analysis revealed four key themes: (1) intrinsic motivation and personal growth, (2) external support and institutional resources, (3) barriers to research completion, and (4) improving support systems. The findings highlight that intrinsic factors such as personal satisfaction and ambition are crucial for research completion, while external factors like mentorship, institutional resources, and cultural context play significant roles. Identified barriers include imposter syndrome, inadequate supervision, and time management challenges. Enhancing mentorship, strengthening institutional support, and developing student skills are recommended to improve research completion rates.

Conclusion: This review underscores the importance of addressing intrinsic and extrinsic motivational factors to support research completion among graduate students in occupational therapy and related health professions. By implementing targeted strategies that enhance mentorship, provide robust institutional support, and develop essential research skills, graduate programs can significantly improve research outcomes and advance evidence-based practice in health professions.

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Introduction

Graduate education, especially a Master's, requires advanced professional skills, self-directed research, and autonomy in professional practice, as independence is

important in academic programs worldwide. Likewise, the ASEAN Qualifications Reference Framework emphasizes research skills as a crucial aspect of graduate qualifications in the ASEAN region.¹ Moreover, the Philippines emphasizes promoting a research culture in graduate schools, aligning with global trends stressing research competency as a crucial outcome of higher education. A robust research culture in graduate education is essential for enhancing research productivity and achieving desired higher education outcomes.² Early research involvement is vital for enhancing graduate success skills, promoting critical thinking, problem-solving abilities, and deeper engagement with the academic process.³

Master's programs often include research-related courses, but students usually struggle to complete their projects due to motivational factors. Motivational factors such as autonomy, the development of a strong research culture, and early involvement in research are critical in influencing the ability of graduate students to complete their research.⁴ Research project characteristics, such as freedom, workload, and alignment with the supervisor's research, significantly influence graduate study success, with high workload and poor alignment leading to dissatisfaction and higher dropout rates.⁴ Moreover, research competence development can be challenging for students, as they struggle to acquire the necessary skills and navigate the complexities of research, mainly when real-world application is limited.⁵ Likewise, the lack of time, money, and institutional support that South African occupational therapists reported as barriers to participating in research is similar to what happens in the Philippines, emphasizing the necessity of a coordinated national research strategy to address these problems effectively.⁶ Moreover, the Philippines' CMO No. 15 Series 2019 has introduced publication requirements, complicating the academic landscape for students due to inadequate preparation and financial constraints.⁷ Understanding these factors is essential for improving research completion rates and enhancing professional practice, especially in fields like occupational therapy and health professions that rely on evidence-based practice.

This literature review aims to identify and analyze the motivational strategies that facilitate learning and research completion among occupational therapists and other health professions students enrolled in graduate programs. By synthesizing findings from diverse studies, this review seeks to:

1. Identify intrinsic and extrinsic motivational factors that influence research completion.
2. Explore barriers to research completion at the graduate level.
3. Propose motivational strategies graduate programs can adopt to support research completion among occupational therapy and other health professions.

Methodology

Research design

The authors conducted a literature review on motivational strategies in higher education, focusing on

occupational therapy and students from other health professions. This approach allowed a process of identifying, evaluating, and synthesizing data from various sources. In contrast to rigorous methodologies such as scoping or systematic reviews, this literature review provides just an overview of existing knowledge on the topic, ideas, and concepts.⁸

Literature search

The literature search used online databases, including the ASEAN Citation Index, EBSCO, Google Scholar, and Scopus. Initial search terms included combinations of keywords such as "motivational strategies," "graduate education," "occupational therapy," and "research." However, the results did not yield enough relevant studies. Expanded search terms used included combinations of keywords such as "motivational strategies," "graduate education," and "research." Boolean operators (AND, OR) were utilized to refine the search results. The search process was iterative, with refinements made to the search terms to ensure the inclusion of relevant literature. The following were the guiding questions for the literature review:

1. What are the intrinsic and extrinsic motivational factors that influence research completion?
2. What are the barriers to research completion at the graduate level?
3. What motivational strategies can graduate programs adopt to support research completion among occupational therapy and other health professions?

To ensure the relevance and quality of the included studies, the following criteria were applied: (1) Studies published in peer-reviewed journals between 2010 and 2024, (2) Research focused on motivational strategies in graduate education, (3) Studies involving occupational therapy students, health professions students or professionals, and (4) Articles available in English. The following criteria were used to exclude studies: (1) Studies not related to graduate education, (2) non-peer-reviewed articles, such as opinion pieces and editorials, and (3) Publications in languages other than English without available translations. The criteria were applied to literature titles initially searched, followed by further screening through abstracts and full texts. After using these criteria, 17 articles met the inclusion criteria and were selected for review.

Data Analysis

A frequency analysis was used to summarize the articles according to year of publication, geographical location, methodology, data collection method, and population. The authors used thematic analysis⁹ to identify common themes and patterns regarding motivational strategies for research completion in graduate school. Both intrinsic and extrinsic motivational factors were examined. Moreover, the authors did not assess for methodological rigor for the included studies as it is beyond the scope of this review.¹⁰

The following were the steps in analyzing the data. First, the authors began familiarizing themselves with the data by reading and re-reading the full texts of the included studies. Second, the authors independently assigned codes for significant words, phrases, or sentences. During this step, the authors regularly held discussions to settle any conflicts in the coding process. Third, the authors searched for themes by organizing the codes. Patterns, connections, and recurring concepts were the basis for establishing the themes. Fourth, the authors reviewed the themes to ensure they represented the coded data. Fifth, the authors defined and named the final set of themes. Lastly, the authors prepared and reviewed a written report of the findings.

Results

Frequency Analysis

Table 1 shows the results of the frequency analysis of the analyzed articles. Most articles were published between 2020 and 2024, indicating a recent interest in the topic. Asia was the most represented continent, with a significant proportion of studies originating from countries like Hong Kong, China, the Philippines, Vietnam, and India. Most studies utilized quantitative methodologies, while a smaller percentage employed qualitative and mixed methods designs. Data collection methods were predominantly surveys, with other studies incorporating mixed methods, focus groups, and interviews. The research primarily focused on graduate students, including those at the master's, doctoral, and post-doctorate levels, with some studies examining mixed populations of faculty and students.

Table 1. Frequency analysis of articles reviewed.

Category		N / 17 (%)
Year of publication	2020-2024	12 (70.6)
	2010-2014	3 (17.6)
	2015-2019	2 (11.8)
Continent (countries)	Asia (Hong Kong, China, Philippines, Vietnam, India)	7 (41.2)
	Europe (Netherlands, Germany, Sweden)	3 (17.6)
	Oceania (New Zealand)	2 (11.8)
	Africa (Tanzania, South Africa)	2 (11.8)
	Not applicable (Evidence synthesis)	2 (11.8)
	North America (USA)	1 (5.9)
Methodology	Quantitative	7 (41.2)
	Qualitative	5 (29.4)
	Mixed methods	3 (17.6)
	Evidence synthesis (scoping, systematic review)	2 (11.8)
Data collection method	Surveys	7 (41.2)
	Mixed	5 (29.4)
	Focus groups	2 (11.8)
	Interviews	2 (11.8)
	Content analysis	1 (5.9)
Population	Mixed graduate students (Master's, Doctorate, Post-doctorate)	10 (58.8)
	Doctoral students	4 (23.5)
	Mixed (faculty and students)	3 (11.8)

Thematic Analysis

The thematic analysis of the data yielded four key themes that provide insight into the factors influencing research completion among graduate students. These themes cover intrinsic and extrinsic motivational factors, barriers

to research completion, and strategies for enhancing support systems within graduate programs that may apply to occupational therapy and other health professions (Table 2).

Table 2. Summary of themes and sub-themes.

Guiding/research questions	Themes	Sub-themes
1. What are the intrinsic and extrinsic motivational factors that influence research completion?	Intrinsic motivation and personal growth External support and institutional resources	• Personal satisfaction and self-perception • Commitment and ambition • Mentorship and supervision • Institutional resources and infrastructure • Cultural and environmental context
2. What are the barriers to research completion at the graduate level?	Barriers to research completion	• Personal barriers • Institutional barriers • External barriers
3. What motivational strategies can graduate programs adopt to support research completion among occupational therapy and other health professions?	Improving support systems	• Enhancing mentorship and supervision • Strengthening institutional support • Developing student skills

Theme 1: Intrinsic motivation and personal growth

Intrinsic motivation, including personal satisfaction, self-perception, commitment, and ambition, significantly influences graduate students' research completion, emphasizing the importance of these factors in the research journey. Graduate students' satisfaction stems from their roles as educators, researchers, and scholars, bolstered by their self-perception and ambition to achieve academic and professional goals. Intrinsic factors play a crucial role in comprehending how personal factors influence the persistence and success of graduate students in occupational therapy and related health professions.

Sub-theme 1.1: Personal satisfaction and self-perception

Graduate students often find personal satisfaction in their roles as educators, researchers, and scholars, which is closely linked to their perception of themselves within these academic fields. Research is often seen as a way for students to affirm their identity and purpose within the educational community, fostering intrinsic motivation to overcome challenges.¹¹ Self-perception is essential in students' motivation to research despite challenges.^{12,13}

Sub-theme 1.2: Commitment and ambition

Graduate students with ambition and commitment to long-term career aspirations will likely remain focused and driven during the research process.¹⁴ The ambition is frequently the result of a desire to reach significant personal and professional milestones, such as publishing research, contributing to the field, or moving up the academic ladder. Likewise, students with solid professional ambitions are more resilient in research challenges, as their commitment to academic goals motivates them to complete their studies.¹⁵ This sub-theme directly addresses the guiding research question by illustrating how personal ambition and commitment are central to research completion.¹⁶

Theme 2: External support and institutional resources

This theme explores how mentorship, institutional support, and educational and cultural influences critically

motivate graduate students to complete their research. Mentorship, institutional resources, and a supportive artistic environment are crucial for students' motivation and success, providing necessary resources, guidance, and context for sustained research efforts.¹⁷⁻¹⁹

Sub-theme 2.1: Mentorship and supervision

Mentorship and supervision are essential in guiding graduate students through research, providing technical advice, emotional and psychological support, and accountability. Strong mentor-mentee relationships are critical in sustaining student motivation and ensuring the successful completion of research projects. For example, mentoring relationships in occupational therapy significantly impact graduate students' research productivity and completion rates, focusing on extrinsic motivational factors.^{17,20}

Sub-theme 2.2: Institutional resources and infrastructure

The availability and quality of institutional resources, such as funding, research facilities, and access to academic networks, are vital to the research process. Institutions that provide robust support systems enable students to focus on their research without being hindered by logistical or financial concerns. Adequate resources and infrastructure facilitate the research process and reinforce the student's commitment to their work. For example, students with access to well-resourced institutions, such as libraries, research grants, and collaboration opportunities, are more likely to complete their research successfully.¹⁸

Sub-theme 2.3: Cultural and environmental context

The cultural and educational environment in which students conduct research significantly influences their motivation and work completion, with cultural norms, institutional culture, and academic environment potentially supporting or hindering research progress. Understanding these influences is essential for creating supportive conditions that align with students' needs and expectations. Likewise, educational culture and environmental context impact graduate students' research

experiences, emphasizing the significance of a positive environment for research completion.¹⁹

Theme 3: Barriers to research completion

Barriers like imposter syndrome, inadequate supervision, time management, and family obligations can significantly affect students' motivation and research completion. Research completion rates for graduate students are significantly improved by addressing challenges.^{14,21,22}

Sub-theme 3.1: Personal barriers

Personal barriers like imposter syndrome, self-regulation issues, and psychological stress can hinder a student's research progress, leading to procrastination, disengagement, and attrition. For example, imposter syndrome is a prevalent graduate student issue where they feel inadequate, leading to doubts about their research abilities, delays, or withdrawal from their programs.²¹ Likewise, students may also feel that they lack adequate skills in completing research-related tasks, which may lead to discontinuation.²³

Sub-theme 3.2: Institutional barriers

Institutional barriers, such as supervision issues, misalignment between student and institutional goals, and inadequate support services, can create a disconnect between students and their academic environment.

Likewise, inadequate supervision and miscommunication between students and advisors significantly hinder research completion, creating feelings of isolation and uncertainty.²²

Sub-theme 3.3: External barriers

External barriers, such as time management, family obligations, and financial constraints, can hinder students' ability to complete their research, potentially leading to delays or discontinuation. Likewise, time management challenges and external responsibilities, such as part-time work or family duties, significantly impact students' ability to focus on their research.¹⁴ Moreover, external pressures often compete with academic demands, causing difficulties in balancing for graduate students that hinder research completion.

Theme 4: Improving support systems

This theme emphasizes enhancing graduate programs' support systems, including mentorship, institutional support, and student skill development, to boost research completion rates. Strategies enhancing mentorship, strengthening institutional support, and developing research skills effectively address barriers and motivational factors influencing research completion.^{6,14,18}

Sub-theme 4.1: Enhancing mentorship and supervision

Mentorship is critical for research success, and effective strategies include training mentors, clear communication, and structured programs to ensure consistent support throughout the research process. Improving the quality of mentorship can significantly

increase students' confidence, provide clearer guidance, and reduce feelings of isolation. For example, structured mentorship programs are important in assisting students with research challenges, fostering stronger relationships, and ensuring timely completion.^{6,17,24–26}

Sub-theme 4.2: Strengthening institutional support

Graduate programs can enhance research completion by aligning institutional resources and policies with student needs. Institutions that boost research funding, offer flexible timelines, and provide students with the necessary tools and infrastructure are likelier to achieve higher completion rates. Likewise, well-developed support systems in institutions, such as research funding and infrastructure, are critical in empowering students to pursue their research goals.^{18,26}

Sub-theme 4.3: Developing student skills

Aside from providing external support, graduate programs should focus on developing students' skills in critical areas such as time management, self-regulation, and research methodologies. Workshops, seminars, and coaching sessions can enhance students' time and resource management skills, helping them overcome barriers to research completion. Moreover, skill development initiatives focusing on research methodologies and time management effectively enhance research outcomes and project completion.¹⁴

Discussion

This literature review highlights the significant role intrinsic and extrinsic motivational factors play in research completion among graduate students. Intrinsic motivation, driven by personal satisfaction and ambition, is crucial for students' commitment to research, complemented by external support systems like mentorship and institutional resources.

The review identifies barriers to research completion, including imposter syndrome, inadequate supervision, and time management issues, which are prevalent across various educational contexts.^{27,28} This review and external studies emphasize the importance of addressing barriers and implementing contextually relevant support systems for improved research completion rates. Safdari *et al.* and Memarpour *et al.* highlight the need for tailored institutional support,^{27,28} while Bulan stresses the importance of adapting educational practices to local contexts.²⁹ Graduate programs should implement tailored strategies to meet their student's unique needs, thereby enhancing the effectiveness of their support systems in facilitating successful research completion.

Implications for occupational therapy and other health professions

The findings from this literature review have practical implications for improving research completion in occupational therapy and other health professions. Educational programs should enhance mentorship quality and provide robust institutional resources to

tackle common barriers like imposter syndrome and time management issues. Graduate programs should establish structured mentorship programs and ensure students can access the necessary research tools and support services. Adopting these strategies can enhance students' research skills, leading to a more evidence-based and competent workforce in health professions. However, it is essential to recognize the challenges in resource allocation and the need for tailored approaches to meet diverse student needs.

Implications for future research

This review suggests areas for future research to understand better factors influencing research completion among graduate students in occupational therapy and related health professions. Future research should investigate the long-term efficacy of strategies like improved mentorship and tailored institutional support in various educational settings. Likewise, qualitative research could offer a deeper understanding of graduate students' experiences with imposter syndrome and time management issues, thereby enhancing research completion. Future research could also focus on the specific needs of underrepresented student populations and how targeted interventions can support them. Moreover, investigating the role of emerging technologies, such as virtual mentorship programs and online skill development tools, in supporting research completion would also be valuable. Addressing these areas can provide deeper insights and more robust solutions for improving research outcomes across health professions education.

Limitations

While this literature review provides valuable insights into the factors influencing research completion among graduate students, several limitations should be acknowledged. The review was limited to English-published studies in selected databases, potentially excluding relevant research from other languages or less accessible sources. The review's broad focus on graduate students may have overlooked the nuances of occupational therapy and health professions graduate education, potentially limiting the generalizability of the results as more studies were needed for analysis. Finally, the review's reliance on existing literature reflects the scope and quality of the available studies, which may vary.

Conclusion

This literature review examines the factors influencing graduate students' research completion and provides insights into occupational therapy and related health professions. Our findings highlight the critical role of personal motivation, effective mentorship, and institutional support in sustaining research efforts. Barriers such as imposter syndrome, inadequate supervision, and time management challenges were identified as significant obstacles, emphasizing the need for targeted interventions. The review also outlined strategies that graduate programs can implement to enhance research

completion, including improved mentorship, tailored institutional resources, and skill development initiatives. Graduate programs can improve research completion by addressing barriers and providing guidance for educators and researchers, contributing to advancing knowledge and practice in occupational therapy and health professions.

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References

- [1] Association of Southeast Asian Nations [ASEAN]. ASEAN qualifications reference network (AQRF) [Internet]. 2014 [cited 2023 Jul 17]. Available from: <https://asean.org/wp-content/uploads/2017/03/ED-02-ASEAN-Qualifications-Reference-Framework-January-2016.pdf>.
- [2] Reston ED, Jugar, RR. Building a research culture in Philippine graduate education: reflections on experiences in mathematics education. In: Atweh B, Fan L, Vistro-Yu CP (Ed) Asian research in mathematics education. Singapore: Springer; 2023. doi: 10.1007/978-981-99-0643-7_1.
- [3] Owens A, Brien DL, Ellison E, Batty C. Student reflections on doctoral learning: challenges and breakthroughs. Stud Grad and Postdoctoral Educ. 2020; 11(1): 107-22. doi: 10.1108/SGPE-04-2019-0048.
- [4] Adebisi YA. Undergraduate students' involvement in research: values, benefits, barriers and recommendations. Ann Med Surg. 2022; 81. doi: 10.1016/j.amsu.2022.104384.
- [5] Toquero CMD. "Real-world:" preservice teachers' research competence and research difficulties in action research. J Appl Res High Educ. 2021; 13(1): 126-48. doi: 10.1108/JARHE-03-2019-0060.
- [6] Damoco TB. Philippine graduate students' perspectives on CMO No. 15 Series 2019 as basis for a conceptual model. Educ Admin: Theory and Practice. 2024; 3(5): 883-8. doi: 10.53555/kuey.v30i5.2974.
- [7] van Rooij E, Fokkens-Bruinsma M, Jansen E. Factors that influence PhD candidates' success: the importance of PhD project characteristics. Stud Cont Educ. 2021; 43(1): 48-67. doi: 10.1080/0158037X.2019.1652158.
- [8] Pitout H. Barriers and strategies to increase research involvement of South African occupational therapists. S Afr J Occup Ther [Internet]. 2014; 44(2): 17-21. Available from: http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S2310-38332014000200005&lng=en&tlng=en.
- [9] Grant MJ, Booth A. A typology of reviews: an analysis

- of 14 review types and associated methodologies. *Health Info Libr J*. 2009; 26(2): 91-108. doi: 10.1111/j.1471-1842.2009.00848.x.
- [10] Peters MD, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Scoping reviews. In: *JBIM Manual for Evidence Synthesis*. JBI; 2024.
- [11] Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006; 3(2): 77-101. doi: 10.1191/1478088706qp063oa.
- [12] Campbell F, Tricco AC, Munn Z, Pollock D, Saran A, Sutton A, et al. Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different- the "Big Picture" review family. *Syst Rev*. 2023; 12: 45. doi:10.1186/s13643-023-02178-5.
- [13] Brooks JV, Dickinson BL, Quesnelle KM, Bonaminio GA, Chalk-Wilayto J, Dahlman KB, et al. Professional identity formation of basic science medical educators: A qualitative study of identity supports and threats. *Acad Med*. 2023; 98(11S): S14-S23. doi: 10.1097/ACM.0000000000005354.
- [14] Van Bragt CAC, Bakx AWEA, Bergen TCM, Croon MA. Looking for students' personal characteristics predicting study outcome. *High Educ*. 2011; 61: 59-75. doi: 10.1007/s10734-010-9325-7.
- [15] Gamage KAA, Dehideniya DMSCPK, Ekanayake SY. The role of personal values in learning approaches and student achievements. *Behav Sci*. 2021;11(7):102. DOI: 10.3390/bs11070102.
- [16] Lindahl J. Conscientiousness predicts doctoral students' research productivity. *J Informetr*. 2023; 17(1): 101353. doi: 10.1016/j.joi.2022.101353.
- [17] Jung J, Li X. Exploring motivations of a master's degree pursuit in Hong Kong. *Higher Educ Q*. 2021; 75: 321-32. doi:10.1111/hequ.12276.
- [18] Amani J, Myeya H, Mhewa M. Understanding the motives for pursuing postgraduate studies and causes of late completion: supervisors and supervisees' experiences. *Sage Open*. 2022; 12(3). doi: 10.1177/21582440221109586.
- [19] Chang JC, Wu YT, Ye JN. A study of graduate students' achievement motivation, active learning, and active confidence based on relevant research. *Front Psychol*. 2022; 13. doi: 10.3389/fpsyg.2022.915770.
- [20] Mosykowski EA, Daly SR, Peters DL. Drivers of research topic selection for engineering doctoral students. *Int J Eng Educ [Internet]*. 2017; 33(4): 1283-96. Available from: <https://dalyresearch.engin.umich.edu/wp-content/uploads/sites/237/2018/02/Drivers-of-research-topic-selection-for-engineering-doctoral-students.pdf>.
- [21] Carra KA, Fortune T, Ennals P, D'Cruz K, Kohn H. Supporting scholarly identity and practice: Narratives of occupational therapy academics. *Brit J Occup Ther*. 2017;80(8):502-9. doi:10.1177/0308022617700653.
- [22] Shahsavari Z, Kourepaz H. Postgraduate students' difficulties in writing their theses literature review. *Cogent Educ*. 2020; 7(1): 1784620. doi: 10.1080/2331186X.2020.1784620
- [23] Le M, Pham L, Kim K, Bui N. The impacts of supervisor-PhD student relationships on PhD students' satisfaction: a case study of Vietnamese universities. *J Univ Teach Learn Prac. [Internet]*. 2021; 18(4). Available from: <https://ro.uow.edu.au/jutlp/vol18/iss4/18>.
- [24] Abdul Rauf FH. Challenges of thesis work: towards minimizing the non-completion rate in the postgraduate degree program. *Eur J Bus Manag. [Internet]*. 2016; 8(7). Available from: <https://iiste.org/Journals/index.php/EJBM/article/view/29456>.
- [25] Jiranek V. Potential predictors of timely completion among dissertation research students at an Australian faculty of sciences. *Int J Doctoral Stud*. 2010; 5: 1-13. doi: 10.28945/709.
- [26] Virtanen P, Nevgi A, Niemi H. Self-regulation in higher education: students' motivational, regulational and learning strategies, and their relationships to study success. *Stud Learn Soc*. 2015; 3(1-2): 20-36. doi: 10.2478/sls-2013-0004.
- [27] Doyle NW, Gafni Lachter L, Jacobs K. Scoping review of mentoring research in the occupational therapy literature, 2002-2018. *Aust Occup Ther J*. 2019; 66(5): 541-51. doi: 10.1111/1440-1630.12579.
- [28] Quimbo MAT, Sulabo EC. Research productivity and its policy implications in higher education institutions. *Stud High Educ*. 2014; 39(10): 1955-71. doi: 10.1080/03075079.2013.818639.
- [29] Quitoras MCL, Abuso JE. Best practices of higher education institutions (HEIs) for the development of research culture in the Philippines. *Pedagogical Res*. 2021; 6(1): em0087. doi: 10.29333/pr/9355.

The roadblocks to business ownership: Analyzing the challenges Thai physical therapists face despite entrepreneurial education

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ABSTRACT

Background: The field of entrepreneurship poses significant challenges for undergraduate students and physical therapists in Thailand. Entrepreneurial intention, entrepreneurial courses in the physical therapy curriculum, and personality qualities are likely the prominent influencers. The social-environmental factors, access to resources, and perceptions of opportunity are also suggested to play a role of the secondary influencers on entrepreneurship. Regrettably, there is a lack of empirical evidence about the impact of these effects on entrepreneurial concepts within physical therapy.

Objective: This study aimed to ascertain the mutual correlation and assess the primary and secondary influencers for entrepreneurship among undergraduate students and physical therapists.

Materials and methods: A cross-sectional study was conducted on 120 physical therapy students and general physical therapists. An online, structured questionnaire with a five-point Likert scale for primary and secondary influencing factors was designed. All questions' content validity and reliability were determined before being applied to all respondents, and a significant relationship was identified with Barlette's test. The Kaiser-Meyer-Olkin Measure (KMO) and the measure of sample adequacy (MSA) were used to assess the overall feasibility of factorial analysis. Finally, the IBM SPSS AMOS program analyzed the influence on entrepreneurship with structural equation modeling (SEM).

Results: The results from 120 responses (74 females and 46 males), 64 undergraduate students, and 56 general physical therapists were 25.81±6.62 years (21-51 years old). All questions showed good reliability. All influencing factors showed a significant relationship and feasibility through factor analysis (FA). Furthermore, the primary factors showed that personality traits strongly influenced entrepreneurship compared to entrepreneurial intention. However, the curriculum had a meager impact. In addition, secondary influencing factors, such as opportunity perception, access to resources, and social-environment factors, highly influence entrepreneurship.

Conclusion: Personality traits and entrepreneurial intention are the most influencing factors, but the course in the curriculum is less influential for entrepreneurship. On the other hand, opportunity perception, access to resources, and social/environmental factors are also the secondary strong influencing factors among physical therapy students and general physical therapists.

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Introduction

Entrepreneurship is essential for a new generation, as is the transition strategy of many education institutions worldwide. Chiang Mai University in Thailand is becoming a prominent catalyst for national progress. It accomplishes this by training competent and skilled individuals in

the entrepreneurial field who can provide answers and significantly contribute to advancing entrepreneurship education by nurturing a generation of well-informed entrepreneurs.¹ University students, like their counterparts in Malaysia and other countries, are required to enter the workforce upon completing their studies. Additionally, some students can transition into entrepreneurship.² In recent years, there has been a notable growth in interest in entrepreneurship among undergraduate and postgraduate students.³ According to Voda and Florea (2019), entrepreneurship has become a compelling career choice for undergraduates worldwide. It has reached a new height among university graduates and post-graduate students at Chiang Mai University, which has only recently designed its curriculum from 2024 to 2030.⁴ Despite the university's promotion of a new campaign or selected short courses related to entrepreneurship or business as a lifelong learning channel, the professional graduate program of physical therapy has maintained a fixed course syllabus for a long time without adding any subjects related to entrepreneurship or business. This could pose a significant obstacle for graduate students seeking to enhance their academic performance. According to many experts, entrepreneurship stimulates interest, passion, and entrepreneurial interest among youth.⁵ As a result, the university should play an essential role in stimulating students' entrepreneurial intentions; one way to do this is to provide entrepreneurship education. A conceptual model and the Theory of Planned Behavior (TPB) organize the components that influence entrepreneurial intention.^{6,7} Primarily, the approach distinguishes between internal and external causes. Internal factors can influence career choices primarily determined by models identifying individual characteristics and consistent behavior patterns.⁸ Entrepreneurship is influenced by personal characteristics such as personality traits, risk-taking propensity, achievement orientation, locus of control,⁹ access to resources that can significantly influence success and sustainability, and the opportunity perception of the business.¹⁰ External factors focus on

social, economic, and educational aspects. A contextual variable can influence an individual's intention to be an entrepreneur. External factors affect students' decisions at university and their didactic activities.⁶ A previous study reported that education is the most critical element contributing to students' intention to start a company. The scarcity of jobs has forced the youth to compete for these positions.¹¹ Unemployment rates continue to rise as job seekers exceed the supply.¹² Previous evidence suggests that entrepreneurship education positively impacts students' entrepreneurial intentions.¹³ From the perspective of both external and internal factors, education in course curriculum (C), personality trait (PT), and entrepreneurial intention (ET) should have a mutual relationship for entrepreneurship, as shown in the previous study in Romania⁴ and Malaysia.¹⁴ Moreover, the social/environmental factor (SE), access to resources (AR), and opportunity perception (OP) are also relationships together for business start-ups, which can change with different directions to entrepreneurship.¹⁵ But, these factor relationships have not been approved among physical therapists in Thailand, which are developing in the future, as contrast evidence to building and changing business models among Dutch physiotherapy primary healthcare organizations.¹⁶ Therefore, this study aimed to assess the relationship between influencing factors, either primarily factors such as personality traits, entrepreneurial intention, and entrepreneurial courses in the Bachelor's curriculum, or the social and environmental factors, access to resources, and opportunity perceptions of entrepreneurship as the secondary influencing factors among physical therapy students and physical therapists in Thailand as a concept framework in Figure 1. The results from this study on the mutual relationship between either primary influencing factors or secondary factors and influences possibly reflect the entrepreneurship trends among undergraduate students and general physical therapists that may benefit the global education policy on entrepreneurship.

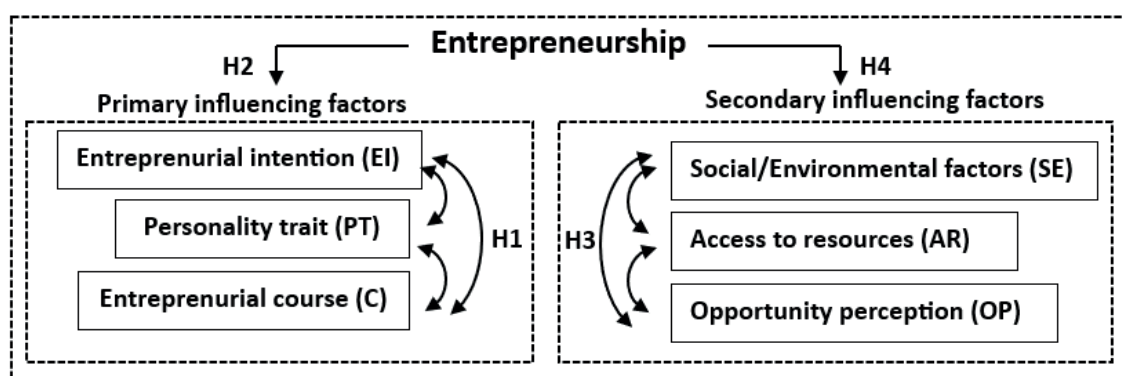


Figure 1. Hypothesis development framework on primary and secondary influencing factors related to entrepreneurship.

Hypothesis development primary influencing factors

- H1: entrepreneurial intention (EI), entrepreneurial course (C), and personality trait (PT) had a positive mutual relationship.
- H2: entrepreneurial intention (EI), entrepreneurial course (C), and personality trait (PT) had a different influence on entrepreneurship.

Hypothesis development on secondary influencing factors

- H3: social and environmental factors (SE), access to entrepreneurial resources (AR), and opportunity perception (OP) had a positive mutual relationship.
- H4: social and environmental factors (SE), access to entrepreneurial resources (AR), and opportunity perception (OP) had a different influence on entrepreneurship.

Methodology

This study conducted an online survey using Google Forms, targeting fourth-year physical therapy students and general physical therapists through an invitation letter and QR Code. The Human Ethical Committee at the Faculty of Associated Medical Sciences, Chiang Mai University, Thailand, approved the study protocol before initiating the data collection (AMS-Ex67-020). Before the respondents agreed to answer the questionnaires, they clearly understood the research details in the subject information sheet and submitted their e-signature online in Google Forms.

Sample size calculation

Minimum sample size estimation is one of the most fundamental issues in structural equation modeling (SEM). The "10-times rule" method is a common way to determine the minimum sample size for SEM.¹⁷ It is based on the idea that the sample size should be more than 10 times the number of inner or outer model links that point to any latent variable in the model. Although PLS-SEM users favor this method for its ease of application, Goodhue *et al.* have demonstrated that it can result in inaccurate estimates.¹⁸ Therefore, the accessible population applied to all 120 students and physical therapists because the ratio of primary influencing factor questions and respondents was 1:10 from the minimal sample size estimation.

Outcomes and Instruments

All respondents completed questionnaires using a five-point Likert scale ranging from strongly agree (5 marks) to strongly disagree (1 mark). Three items of primary influencing factors, namely personality traits (PT), entrepreneurial intention (EI), and entrepreneurial course in the curriculum (C), dominate a structured 24-questionnaire. Secondary influencing factors include social and environmental factors (SE), access to resources (AR), and opportunity perception (OP), all of which have an impact on entrepreneurship. Two qualitative research experts, along with a pilot study of 30 students, rechecked the content validity of all the well-structured, closed-ended questionnaires and the reliability of the questions

by calculating Cronbach's alpha coefficient, which should be greater than 0.7.¹⁹

Entrepreneurial intention^{20,21}

- EI1: I strongly desire to start my own business in the future.
- EI2: I am actively exploring entrepreneurial opportunities and ideas.
- EI3: I am committed to pursuing entrepreneurship as a career path.
- EI4: I have the necessary skills and knowledge to be a successful entrepreneur.

Personality trait^{20,21}

- PT1: I enjoy leading and motivating others toward common goals.
- PT2: I am adaptable and able to adjust to changing circumstances.
- PT3: I am creative and innovative in solving business challenges.
- PT4: I communicate effectively with stakeholders in my business.

Entrepreneur course in the curriculum²²

- C1: Some entrepreneurial courses have been taught to me.
- C2: The entrepreneurship course I took at the university has taught me to develop a business owner in the future.
- C3: The entrepreneurship course has taught me to develop business plans successfully.
- C4: The entrepreneurship course has taught the essential business skills (C4).

Social and environmental factors^{20,21}

- SE1: My future business will have values and promote social responsibility and ethical practices.
- SE2: I will have strong relationships with our customers and prioritize customer satisfaction.
- SE3: My future business will comply with environmental regulations and strive to exceed minimum standards.
- SE4: My future business will invest in technologies or innovations that improve our environmental performance and efficiency.

Access to resources for entrepreneurship²³

- AR1: I can access sufficient financial resources to pursue entrepreneurial opportunities.
- AR2: I can access mentorship or guidance from experienced entrepreneurs or business professionals.
- AR3: I can access networks or connections that can help me access opportunities, resources, or support.
- AR4: I can access information and knowledge about entrepreneurship and business management.

Opportunity perception for entrepreneurship²³

- OP1: There are abundant entrepreneurial opportunities in the market.

OP2: I perceive potential gaps or unmet needs in the market that could be addressed through entrepreneurship.

OP3: I am confident in identifying and evaluating promising entrepreneurial opportunities.

OP4: I see entrepreneurship as a means to create value and positively impact society.

Statistical analysis

All questionnaires were rechecked for the validity of the questions from an index of item-objective congruence (IOC) by three survey experts. The index was computed using the item congruence index to measure the agreement with a rating of +1 (clearly does measure the objective), 0 (unclear), and -1 (clearly does not measure the objective) in each item. The result indicates the IOC indices for all the items rated by the three experts ranged from 0.33 to 1.0. The IOC within 0.5 to 1.00 indicates acceptable and is to be retained for measurement.²⁴ Whereas, the reliability of questionnaires was approved by Cronbach's alpha coefficient, which should be greater than 0.7.¹⁹ The feasibility of all influences that could be suitable through the fit model in structural equation modeling (SEM) analysis was evaluated with confirmatory factor analysis (CFA) from the Kaiser-Meyer-Olkin Measure (KMO) ($p < 0.05$)

and the average of Measures of Sample Adequacy (MSA) (> 0.5).²⁵ Then, a fit model was evaluated the relative Chi-Square (χ^2), goodness-of-fit index (GFI), normal fit index (NFI), Tucker-Lewis index (TLI), comparative fit index (CFI), root mean square error of approximation (RMSEA), and root mean square residual (RMR). The final fit models can be declared the model's suitability if they have a relative χ^2 below 2.0, GFI, NFI, TLI, and CFI values above 0.9, and RMSEA and RMR values below 0.05.²⁶ In addition, the level of influence of each factor on entrepreneurship can be identified from a saturated estimate value. The IBM® SPSS® AMOS 23.0.0 (USA) software was used for statistical analysis.

Results

Twenty-four questionnaires from 30 respondents showed good reliability for each item and question. The Cronbach's alpha coefficient for all 24 questionnaires is 0.897. It's acceptable for each item questionnaire: (1) intention to start a business (0.780), (2) course support in the curriculum (0.947), (3) personality traits (0.903), (4) social and environmental factors (0.872), (4) access to resources (0.789), and (5) opportunity perception (0.747), (Table 1).

Table 1. The reliability of each item in each questionnaire (N=30).

Items	Questions	Cronbach's Alpha
Entrepreneurial intention (EI)	EI1	0.894
	EI2	0.895
	EI3	0.890
	EI4	0.892
Entrepreneurial course in the curriculum (C)	C1	0.896
	C2	0.892
	C3	0.891
	C4	0.893
Personality traits (PT)	PT1	0.892
	PT2	0.893
	PT3	0.897
	PT4	0.895
Social/Environmental factor (SE)	SE1	0.896
	SE2	0.894
	SE3	0.897
	SE4	0.893
Access to resources (AR)	AR1	0.898
	AR2	0.895
	AR3	0.889
	AR4	0.891
Opportunity perception (OP)	OP1	0.890
	OP2	0.889
	OP3	0.890
	OP4	0.889

Table 2 presents the data of all 120 respondents. From the 120 respondents (74 females and 41 males), there are fourth-year students (N=64) and general physical therapists (N=56). The mean age was 25.8 ± 6.62 (21-51 years old). The family or respondents' occupations were classified into three items: non-related business (N=92, 76.7%), general business (N=19, 15.8%), and physical therapy clinic (N=9, 7.5%). The intention to pursue entrepreneurship included an interest in becoming a business owner (N=17, 14.2%), an interest but unsure

of being an entrepreneur (N=80, 66.7%), a non-related physical therapy business (N=5, 4.2%), a physical therapy business (N=9, 7.5%), and an uninterest in business (N=9, 7.5%). Finally, the prior learning on entrepreneurial courses showed the most learning in a free-elective course (N=67, 55.8%), whereas learning in the main course in the curriculum (N=25, 20.8%), other courses (N=13, 10.8%), and no learning from any courses (N=15, 12.5%), respectively.

Table 2. The primary data of 120 respondents.

Respondents	120
Undergraduate physical therapy students	64
General physical therapists	56
Gender: females/males	74:46
Aged (years)	25.8 ± 6.62 (21-51)
Family occupation	
Non-related business job	92 (76.7%)
General business	19 (15.8%)
Physical Therapy clinic	9 (7.5%)
Intention in entrepreneurship	
Interest and expect to be an entrepreneurship	17 (14.2%)
Interest but unsure to be an entrepreneurship	80 (66.7%)
Interest in non-related physical therapy business	5 (4.2%)
Physical therapy business	9 (7.5%)
No at all in business	9 (7.5%)
Entrepreneurial course learning	
Main course in the Bachelor's curriculum	25 (20.8%)
Free elective course in the Bachelor's curriculum	67 (55.8%)
Other courses from the Bachelor's curriculum	13 (10.8%)
Never Learned	15 (12.5%)

Relationship between influencing factors for fit model analysis

The results of the relationship analysis between three items of primary influencing factors curriculum (C), personality traits (PT), and EI evaluated with Bartlett's Test of Sphericity showed that all had a significant relationship (>0.5). The KMO showed the overall feasibility of all influences, revealing an average sample adequacy (MSA) of 0.841 and individual values ranging from 0.741 to 0.898 (Table 3). Therefore, we can conclude that all influencing factors are viable for analyzing the goodness-of-fit model to predict entrepreneurship. In addition, the other

three items of secondary influencing factors—social/environmental factors (SE), access to resources (AR), and opportunity perception (PO)—were all found to have a significant correlation at 0.05. The overall feasibility of all influences can be assessed through the confirmatory factor analysis (CFA) with the Kaiser-Meyer-Olkin Measure (KMO), which showed an average of measures of sample adequacy (MSA) at 0.796 and an individual value within 0.712 to 0.876 (Table 4) that was more than 0.5.¹⁷ Therefore, we can conclude that the goodness-of-fit model can analyze all secondary influences to predict entrepreneurship.

Table 3. Relationship between all influencing factors from 120 respondents.

Influencing factors	EI1	EI2	EI3	EI4	C1	C2	C3	C4	PT1	PT2	PT3	PT4
EI1	0.806^a											
EI2	-0.446	0.824^a										
EI3	-0.389	-0.379	0.856^a									
EI4	-0.157	-0.080	-0.121	0.848^a								
C1	0.010	0.020	0.091	0.026	0.895^a							
C2	-0.252	0.262	0.096	-0.214	-0.201	0.804^a						
C3	0.059	-0.037	-0.274	0.316	-0.370	-0.550	0.741^a					
C4	0.219	-0.159	0.124	-0.311	0.064	-0.069	-0.557	0.792^a				
PT1	0.014	0.116	-0.117	-0.237	0.027	-0.044	-0.038	0.085	0.883^a			
PT2	0.014	-0.031	-0.071	-0.076	-0.154	0.181	0.006	-0.108	-0.348	0.871^a		
PT3	0.171	-0.123	-0.088	-0.050	0.061	-0.110	-0.108	0.120	-0.046	-0.282	0.875^a	
PT4	-0.130	-0.046	0.097	-0.116	0.033	0.011	-0.058	0.068	-0.149	-0.121	-0.351	0.898^a

Bartlett's test=0.796, Sig=0.000, KMO=0.841, MSA between 0.741 to 0.898.

Note: a: measures of sampling adequacy (MSA), C: curriculum, PT: personality traits, E: entrepreneurial intention.

Table 4. Relationship between all influencing factors from 120 respondents.

Influencing factors	SE1	SE2	SE3	SE4	AR1	AR2	AR3	AR4	OP1	OP2	OP3	OP4
SE1	0.830^a											
SE2	-0.541	0.769^a										
SE3	-0.137	-0.232	0.777^a									
SE4	-0.011	0.001	-0.578	0.738^a								
AR1	0.193	-0.192	0.146	-0.198	0.743^a							
AR2	-0.122	0.270	-0.098	0.033	-0.143	0.838^a						
AR3	-0.032	-0.118	0.028	-0.113	-0.264	-0.417	0.837^a					
AR4	-0.096	0.017	-0.061	0.213	-0.189	-0.031	-0.311	0.871^a				
OP1	0.059	-0.144	0.157	0.074	-0.160	-0.012	0.165	-0.057	0.712^a			
OP2	0.060	0.004	0.061	-0.106	0.103	-0.105	-0.110	-0.048	-0.183	0.876^a		
OP3	-0.252	0.143	-0.190	0.119	-0.545	-0.025	0.037	0.081	0.053	-0.377	0.796^a	
OP4	-0.045	-0.299	0.039	-0.075	0.272	-0.353	0.154	-0.223	-0.357	-0.093	-0.122	0.775^a

Bartlett's test = 0.762, Sig = 0.000, KMO = 0.796, MSA between 0.712 to 0.876.

Note: a: measures of sampling adequacy (MSA), SE: social/environmental factor, AR: access to resources, OP: opportunity perception.

Goodness-of-Fit model and structural equation modeling result

The goodness-of-fit model was analyzed with the structural equation model (SEM), or model testing, which can predict the influencing factors, either primary or secondary, on entrepreneurship. The SEM analysis result, EI4, revealed a saturated estimate of less than 0.7, prompting the exclusion of the question before analyzing

the model fit. The influence analysis can be concluded in Table 5 that personality traits ($\beta_i=1.06$), how people see opportunities ($\beta_i=0.96$), how easy it is to get resources ($\beta_i=0.81$), and social-environment factors ($\beta_i=0.74$) all have a significant effect on starting a business. Whereas entrepreneurial intention ($\beta_i=0.61$) and entrepreneurial courses in the curriculum ($\beta_i=0.38$) showed a lower influence.

Table 5. Goodness-of-Fit model.

Goodness-of-Fit model	β_i	b_i	SE	R^2
Primary influencing factors				
Entrepreneurial intention (EI)	0.61	0.37	0.30	0.37
Curriculum (C)	0.38	0.32	0.30	0.15
Personality traits (PT)	1.06	1.00	0.00	1.13
$\chi^2=29.176$; $df=35$; relative $\chi^2=19.176$; $p=0.745$; GFI=0.961; NFI=0.971; TLI=1.00; CFI=1.00; RMSEA=0.000; RMR=0.035				
Secondary influencing factors				
Social/Environmental factor (SE)	0.74	0.64	0.110	0.44
Access to resources (AR)	0.81	0.91	0.137	0.63
Opportunity perception (OP)	0.97	0.97	0.133	0.94
$\chi^2=90.581$; $df=72$; relative $\chi^2=90.581$; $p=0.069$; GFI=0.913; NFI=0.921; TLI=0.974; CFI=0.982; RMSEA=0.047; RMR=0.036.				

The suitability SEM of primary influencing factors was $\chi^2=29.176$; $df=35$; relative $\chi^2=19.176$; $p=0.745$; GFI=0.961; NFI=0.971; TLI=1.00; CFI=1.00; RMSEA=0.000; RMR=0.035 (Figure 2). Three influencing factors in Table 5 documented that the personality trait is a well-factor fit for the model ($R^2=1.13$) when compared to entrepreneurial intention ($R^2=0.37$) and curriculum ($R^2=0.15$). A deep evaluation of each question reveals a strong evaluation of E1 to EI3,

with standardized regression weights of 0.90 and 0.89. The C3, C2, C4, and C1 can evaluate the curriculum course with standardized regression weights of 0.98, 0.91, 0.86, and 0.82, respectively. On the other hand, The results of personality trait showed series standardized regression weights of 0.80, 0.75, 0.72, and 0.64 in PT3, PT4, PT2, and PT1.

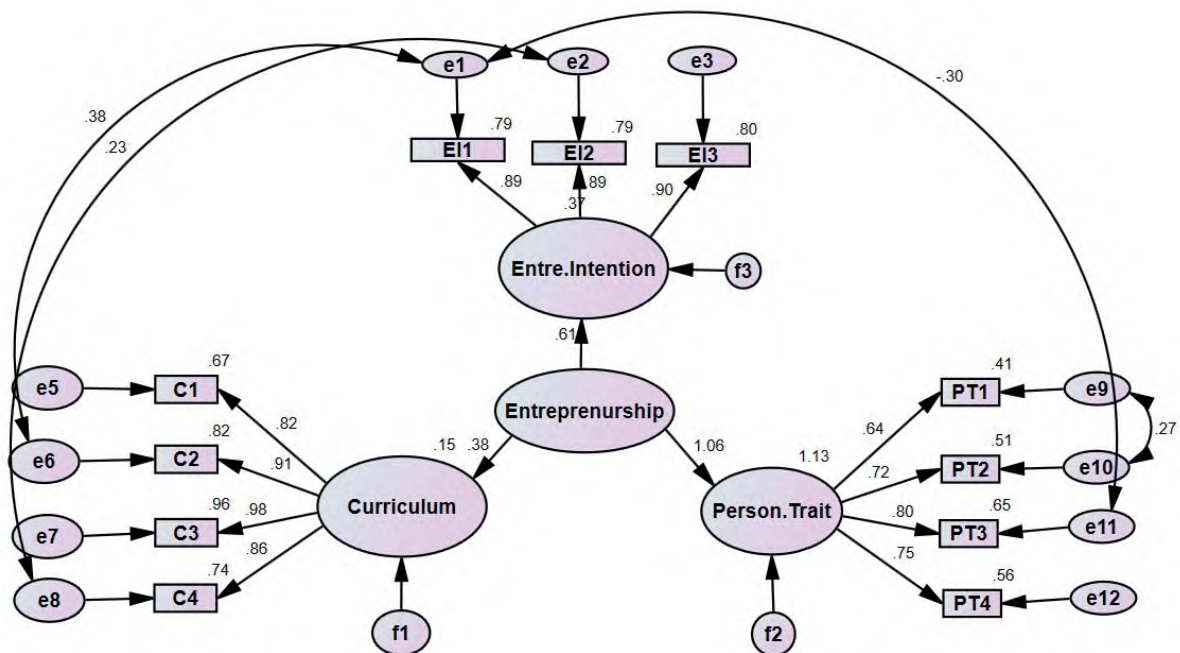
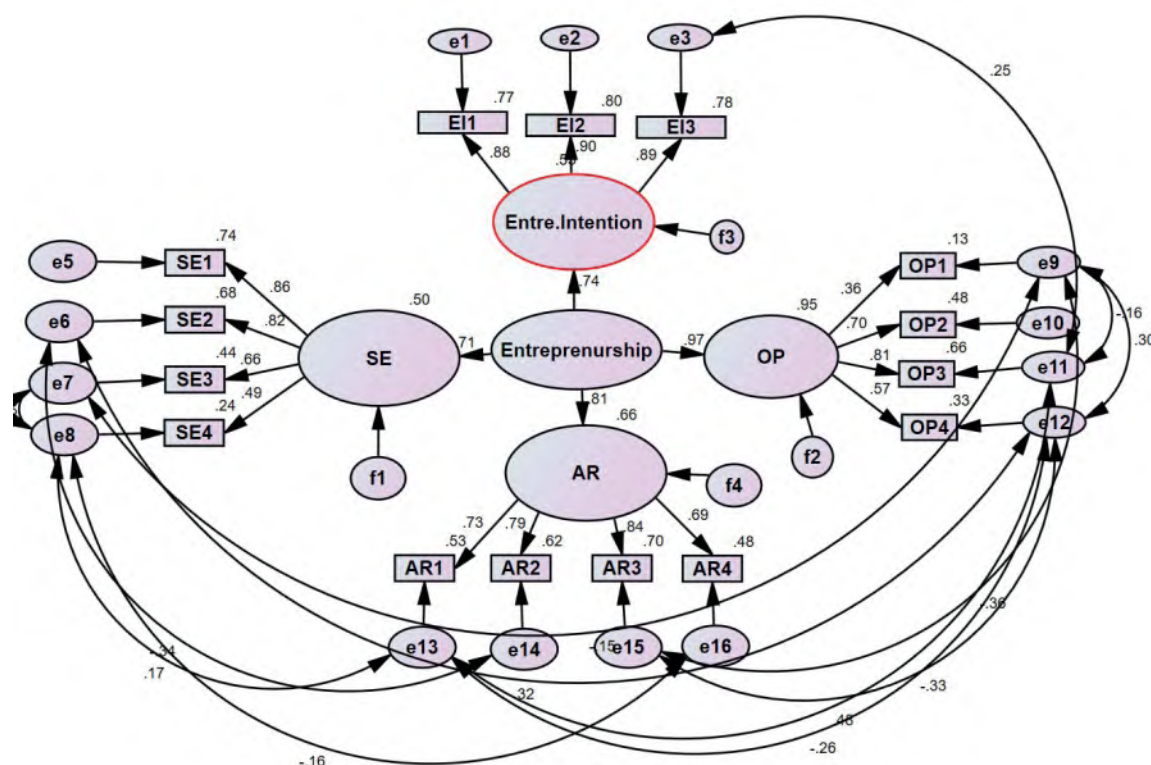


Figure 2. Path diagram of structural equation model (SEM) analysis in the primary influencing factors: entrepreneurial intention, the entrepreneurial course in the curriculum, and personality traits among 120 respondents.

Moreover, the suitability SEM of secondary influencing factors was $\chi^2=90.581$; $df=72$; relative $\chi^2=90.581$; $p=0.069$; GFI=0.913; NFI=0.921; TLI=0.974; CFI=0.982; RMSEA=0.047; RMR=0.036 (Figure 3). In Table 5, three influencing factors documented that opportunity perception (OP) is a good factor fit for the model ($R^2=0.94$) when compared to access to resources ($R^2=0.63$) and social-environmental factors (SE) ($R^2=0.44$). The path

diagram analysis reveals that we can evaluate social and environmental factors from SE1, SE2, SE3, and SE4 with standardized regression weights of 0.86, 0.82, 0.66, and 0.49. In addition, access to resources (AR) results showed the AR3, AR2, AR1, and AR4 at 0.84, 0.79, 0.73, and 0.69. Finally, the opportunity perception(OP) on entrepreneurship showed that OP3, OP2, OP4, and OP1 were 0.81, 0.70, 0.47, and 0.36, respectively.



latent variables represent the structural model through their correlation.³² The consistency theory in this study suggests that we can apply SEM analysis to assess the correlation and factors that influence entrepreneurship among physical therapists. Moreover, selecting a retention criterion from the MSA value is a crucial decision that precedes factor analysis in this study.³³ The maximum likelihood factor extraction method (ML) is one of many techniques used to identify the final factors based on the various model fit indexes as the root mean square error of approximation (RMSEA).³⁴

Goodness-of-Fit model

The path diagram on entrepreneurship, derived from primary and secondary influencing factors, illustrates the program's final modified or revised model, which is determined by observing the value of all goodness-of-fit metrics. This study evaluated the model using the goodness-of-fit index (GFI), normal fit index (NFI), Tucker-Lewis index (TLI), comparative fit index (CFI), root mean square error of approximation (RMSEA), and root mean square residual (RMR). We can declare fit models suitable if they have a relative χ^2 below 2.0, GFI, NFI, TLI, and CFI values above 0.9, and RMSEA and RMR values below 0.05.²⁶ The basic interpretation suggested the Chi-Square (χ^2) for good fit should be between 0 and less than 2df,³⁵ and the GFI, CFI, NFI, and TLI values range from 0-1, with a higher value indicating a better fit.³⁶⁻³⁸ Conversely, values near zero for RMSEA and RMR indicate a robust model fit.³⁹ Therefore, this result showed the accepted model fit.

The suitability model for entrepreneurship among physical therapists includes primary and secondary influence factors. Unsaturated (bi) and saturated estimates (β_i), standard error (SE), and R^2 were reported from model fit analysis and visualized results on the path diagrams.

In this study, personality traits are the strongest influencer when compared to entrepreneurial intention, and the entrepreneurial course in the curriculum has the lowest influence on entrepreneurship among physical therapists, which is consistent with a previous document. Previous evidence suggested that entrepreneurship education positively impacts students' entrepreneurial intentions.¹³ Individual reactions to external conditions or environments can generate personality traits.⁴⁰ A previous report claimed that personality traits are directly related to entrepreneurial intention.⁴² This study didn't evaluate the direct effect of both. In this study, the personality traits are strongly associated with entrepreneurship, similar to a previous study on students in Pakistan.⁴³ Moreover, the primary factors influencing entrepreneurship are courses in the curriculum related to business start-ups among students in Romania⁴ and Malaysia.¹⁴ The other result of the entrepreneurial course in the curriculum showed the lowest saturated estimate (β_i) on the model related to entrepreneurship among physical therapists. However, a previous study proposed that entrepreneurship curricula delivery can improve entrepreneurs' abilities and mindsets.⁴³ The findings of this study among physical therapists stand in contrast, possibly due to the influence

of the previous curriculum. Approximately 50% of the 120 respondents, or physical therapists, were general physical therapists who underwent the curriculum without the entrepreneurial course. Therefore, the entrepreneurial course in the study had a minimal impact on the final model. Finally, most family occupations unrelated to business account for the moderate influence of entrepreneurial intention among physical therapists on entrepreneurship. Thai family culture mainly exhibits less interest in business during economic downturns. Previous evidence suggests that cross-cultural differences in developing countries influence the reported entrepreneurial intention among undergraduate students, supporting these results.⁴⁴

The study recruited business ideas, social-environmental factors, resource access, and opportunity perception as secondary influencing factors. In the SEM analysis on the secondary influencing factors, the results revealed the excellent influence of opportunity perception and access to resources that believed the opportunity and potential gaps for business in the market. Moreover, the respondents have access to mentorship, guidance, networks, and connections that can help them access opportunities, resources, and support. Numerous cooperative departments have existed in Thailand, including the National Science and Technology Development Agency (NSTDA), which has developed Business and Entrepreneurial Acceleration Programs and Special Units within universities to foster advanced entrepreneurship. However, the suitability model's business results on social and environmental factors showed a high influence factor on entrepreneurship with value, promoting social responsibility, and a strong relationship with customers and satisfaction. However, environmental factor (SE), access to resources (AR), and opportunity perception (OP) related to business start-ups among students and physical therapists have been fewer facilities or regulations; thus different directions to entrepreneurship were contrasted in the previous recommendation.¹⁵

Moreover, among physical therapists in Thailand, business technologies or innovations had the least influence. Owner-owned businesses in physical therapy clinics have received less attention than small businesses in the United States, which were reported for brand awareness, relationship marketing, perceived quality, online marketing, and WOM marketing.⁴⁵ Therefore, valuing and promoting social responsibility, strong relationships with customers, and satisfaction in physical therapy clinics will be significant in Thailand in the future.

The survey data from 120 respondents proposed that most knowledge (67, or 55.8%) had studied entrepreneurship in the free-elective course, whereas only 20% (N=25) studied in the main course within the curriculum. In addition, some respondents learned about entrepreneurship from an outside program (10.8%) or had not studied it (12.5%). Thus, this evidence indicates that entrepreneurship among physical therapy students and physical therapists still needs to be more common in universities. The role of educational government must encourage entrepreneurship education in all universities, as the

previous suggestion,⁴⁶ meant that the principal education on physical therapy courses at Chiang Mai University was unsuccessful. Moreover, the entrepreneurship mindset among students and physical therapists still needs to be determined because the extra-open-end interview results support the idea that entrepreneurship knowledge and skills may be constructed in free electives (49.2%) or main curriculum courses (41.7%). Therefore, this means that entrepreneurship is still unnecessary for physical therapists in the future, and the respondents proposed that entrepreneurship skills are still not required.

Conclusion and suggestions

Personality traits and entrepreneurial intention individually influence the roadblock to business ownership among physical therapy students and physical therapists, whereas the curriculum course has less influence on entrepreneurship. However, opportunity perception, resource access, and social-environment factors have fully supported start-up businesses. Additional informed results from fifty percent of total respondents recommended that entrepreneurship should be taught theory and practice (N=61, 50.8%), whereas others proposed only theory learning without entrepreneurship skill training. Furthermore, the free-elective course ought to include the entrepreneurial course. Encouraging young physical therapists to embark on new entrepreneurial ventures could potentially hinder their chances of success. Finally, we should promote future implementation of the rearranged programs in the leading physical therapy curriculum, either undergraduate or postgraduate, focusing on entrepreneurial experience and essential business skills training.⁴⁷ Finally, other universities and physical therapists in Thailand, such as Central, Eastern, Southern, etc., still study different curriculums. Therefore, it is impossible to summarize these results for generalization precisely; further studies with more extensive sample sizes, including other cultures and economic status, are necessary for confirmation.

Conflict of interest

No conflict of interest

References

- [1] Sholihan K, Wibowo A, Dianta K. The influence of Entrepreneurship Education, Entrepreneurial Knowledge and Entrepreneurial Inspiration on Generation Z's Entrepreneurial Intention. *J Usaha*. 2023; 4(1): 1-19. doi:10.30998/juuk.v4i1.1838.
- [2] Mahmood TMAT, Al Mamun A, Ahmad GB, Ibrahim MD. Predicting entrepreneurial intentions and pre-start-up behavior among Ansa Millennials. *Sustainability*. 2019; 11(18): 4939. doi: 10.3390/su11184939.
- [3] Kim JY, Choi DS, Sung CS, Park JY. The role of problem-solving ability on innovative behavior and opportunity recognition in university students. *J Open Innovat Technol*. 2018; 4: 4. doi: 10.1186/s40852-018-0085-4.
- [4] Voda AI, Florea N. Impact of personality traits and entrepreneurship education on entrepreneurial intentions of business and engineering students. *Sustainability*. 2019; 11: 1192. doi: 10.3390/su11041192.
- [5] Kristiansen S, Indarti N. Entrepreneurial Intention among Indonesian and Norwegian Students. *J Enter Cul*. 2004; 12(1): 55-78. doi: 10.1142/S021849580400004X.
- [6] Franke N, Luthje C. Entrepreneurial Intentions of Business Students: A Benchmarking Study. *Int J Innovat Technol Manag*. 2004; 1(3): 269-88. doi: 10.1142/S0219877004000209.
- [7] Ajzen I. The Theory of Planned Behavior. *Organ Behav Hum Decis Process*. 1991; 50(2): 179-211. doi:10.1016/0749-5978(91)90020-T.
- [8] Krueger NF, Reilly MD, Carsrud A. Competing models for entrepreneurial intention. *J Bus Ventur*. 2000; 15(5-6): 411-32. doi: 10.1016/S0883-9026(98)00033-0.
- [9] Churchill N, Bygrave WD. The Entrepreneurship Paradigm(I): A Philosophical Look at its Research Methodologies. *Entrep Theory Pract*. 1989; 14(1): 7-26. doi: 10.1177/104225878901400102.
- [10] Davidsson P. Determinants of Entrepreneurial Intentions. In RENT IX Workshop in Entrepreneurship Research, Piacenza, P., & Wiklund, J. (2018). "Entrepreneurship: An Introduction." New York: Springer. 1995.
- [11] Ferreira JJM, Raposo M, Rodrigues R, Dinis A, Paco A. A Model of Entrepreneurial Intention: an Application of the Psychological and Behavioral Approaches. *J Small Bus Enterprise Dev*. 2012; 19(3):424- 40. doi: 10.1108/14626001211250144.
- [12] Aloulou WJ. Predicting entrepreneurial intentions of final year Saudi university business students by applying the theory of planned behavior. *J Small Bus Enterprise Dev*. 2016; 23: 1142-64. doi: 10.1108/jsbed-02-2016-0028.
- [13] Martins JM, Shahzad MF, Xu S. Factors influencing entrepreneurial intention to initiate new ventures: evidence from university students. 2023; 12: 63. doi: 10.1186/s13731-023-00333-9.
- [14] Thoti KK. Factors Impacts the Students to Choose Entrepreneurship as their Career of Choice in Malaysia. *Int J Multidis Res Anal*. 2023; 6(4): 1640-8. doi: 10.47191/ijmra/v6-i4-38.
- [15] Omferzel DG, Kusce I. The influence of personal and environmental factors on entrepreneurs' performance. *Kybernetes*. 2013; 42(6): 906-27. doi: 10.1108/K-08-2012-0024.
- [16] Ijntema R, Barten DJ, Duits H, Tjemkes B, Veenhof C. Building and changing business models: a qualitative study among Dutch physiotherapy primary healthcare organizations. *Prim Health Care Res Dev*. 2022; 23: e19. doi: 10.1017/S1463423621000840.
- [17] Hair JF, Ringle CM, Sarstedt M. PLS-SEM: Indeed a silver bullet. *J Market Theory Pract*. 2011; 19(20): 139-51. doi: 10.2753/MTP1069-6679190202.
- [18] Goodhue DL, Lewis W, Thompson R. Research note: Does PLS have advantages for small sample size or non-normal data?. *MIS Quarterly*. 2012; 36(3): 981-1001. doi: 10.2307/41703490.

- [19] Christmann A, Van Aelst S. Robust estimation of Cronbach's alpha. *J Multivar Anal.* 2006; 97(7): 1660-74. doi: 10.1016/j.jmva.2005.05.012.
- [20] Rauch A, Frese M. Let's put the person back into entrepreneurship research: A meta-analysis on the relationship between business owners' personality traits, business creation, and success. *Eur J Work Organ Psychol.* 2007; 16(4): 353-85. doi: 10.1080/13594320701595438.
- [21] Zhao H, Seibert SE, Lumpkin GT. The relationship of personality to entrepreneurial intentions and performance: A meta-analytic review. *J Manag.* 2010; 36(2): 381-404. doi: 10.1177/0149206309335187.
- [22] Kirby DA. Entrepreneurship education: can business schools meet the challenge?. *Educ Train.* 2004; 46(8/9): 510-9. doi: 10.1108/00400910410569632.
- [23] Shane S, Venkataraman S. "The Promise of Entrepreneurship as a Field of Research." *Acad Manag Rev.* 2000; 25(1): 217-26. doi: 10.5465/amr. 2000. 2791611.
- [24] Turner RC, Carlson L. Indexes of item-objective congruence for multidimensional items. *Int J Test.* 2003; 3(2): 163-71. doi: 10.1207/S15327574IJT0302_5.
- [25] Hair JF, Risher JJ, Sarstedt M, Ringle CM. When to use and how to report the results of PLS-SEM. *Eur Bus Rev.* 2019; 31(1): 2-24. doi: 10.1108/EBR-11-2018-0203.
- [26] Nunan D, Black H, Choi J. Teacher empowerment through action research. *Fine Print.* 2019; 42(2): 8-13.
- [27] Bujang MA, Omar ED, Baharum NA. A review on sample size determination for Cronbach's alpha test: a simple guide for researchers. *Malays J Med Sci.* 2018; 25(6): 85-99. doi: 10.21315/mjms2018.25.6.9.
- [28] Heo M, Kim N, Faith MS. Statistical power as a function of Cronbach alpha of instrument questionnaire items. *BMC Med Res Methodol.* 2015; 15: 86. doi: 10.1186/s12874-015-0070-6.
- [29] Boomsma A. Robustness of LISREL against small sample sizes in factor analysis models. In: Joreskog KG, Wold H, editors. *Systems under indirection observation: Causality, structure, prediction (Part I)* Amsterdam, Netherlands: North Holland; 1982. pp. 149-73.
- [30] Tabachnick BG, Fidell LS. *Using Multivariate Statistics*: Pearson Education Inc. Boston, MA. 2007.
- [31] Hair JF, Black WC, Babin BJ, Anderson RE, Tatham RL. *Multivariate Data Analysis*. New Jersey: Pearson University Press. 2006.
- [32] Xiong B, Skitmore M, Xia B. A critical review of structural equation modeling applications in construction research. *Autom Constr.* 2015; 49(Part A): 59-70. doi: 10.1016/j.autcon.2014.09.006.
- [33] Conway JM, Huffcutt AI. A Review & Evaluation of Exploratory Factor Analysis Practices in Organizational Research. *Organ Res Method.* 2003; 6(2): 147-68. doi: 10.1177/1094428103251541.
- [34] Park HS, Dailey RM, Lemus D. The Use of Exploratory Factor Analysis and Principal Components Analysis in Communication Research. *Hum Commun Res.* 2002; 28(4): 562-77. doi: 10.1111/j.1468-2958.2002.tb00824.x.
- [35] Curran PJ, West SG, Finch JF. The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychol Methods.* 1996; 1(1): 16-29. doi: 10.1037/1082-989X.1.1.16.
- [36] Jöreskog KG, Sörbom D. *LISREL 8: Structural Equation Modeling with the SIMPLIS Command Language*. Chicago: Scientific Software International. 1993.
- [37] Bentler PM, Bonett DG. Significance tests and goodness of fit in the analysis of covariance structures. *Psychol Bull.* 1980; 88(3): 588-606. doi: 10.1037/0033-2909.88.3.588.
- [38] Tucker LR, Lewis C. A reliability coefficient for maximum likelihood factor analysis. *Psychometrika.* 1973; 38: 1-10. doi: 10.1007/BF02291170.
- [39] Bentler PM. *EQS structural equations program manual*. Encino, CA: Multivariate Software. 1995.
- [40] Ciavarella MA, Buchholtz AK, Riordan CM, Gatewood RD, Stokes GS. The big five and venture survival: Is there a linkage? *J Bus Ventur.* 2004; 19(4): 465-83. doi: 10.1016/j.jbusvent.2003.03.001.
- [41] Gaddam S. Identifying the relationship between behavioral motives and entrepreneurial intentions: An empirical study based on the perceptions of business management students. *The ICFAIAN J Manag Res.* 2008; 7(5): 35-55.
- [42] Cao Y, Asad MM, Wang L, Naz A, Almusharrat N. Role of personality traits for entrepreneurial intentions of young entrepreneurs: a case study of higher education institution. *Front Psychol.* 2022; 13: 1010412. doi: 10.3389/fpsyg.2022.1010412.
- [43] Balushi SA, Balushi HA. The influence of higher education curriculum on entrepreneurship education. *Proceedings of SOCIOINT 2023-10th International Conference on Education & Education of Social Sciences 19-21 June 2023-Istanbul, Turkey.*
- [44] Celik AK, Yildiz T, Aykanat Z, Kazemzadeh S. The impact of narrow personality traits on entrepreneurial intention in developing countries: a comparison of Turkish and Iranian undergraduate students using ordered discrete choice models. *Eur Res Manag Bus Econ.* 2020; 27(1): 1-31. doi: 10.1016/j.iedeen.2020.100138.
- [45] Daugherty ML. Small business marketing strategies for physical therapy practice owners. *Int J Healthc Manag.* 2021; 14(2): 710-6. doi: 10.1080/20479700.2019.1692505.
- [46] Davey T, Hannon P, Penaluna A. Entrepreneurship education and the role of universities in entrepreneurship: Introduction to the special issue. *Ind High Educ.* 2016; 30(3): 171-82. doi: 10.1177/0950422216656699.
- [47] Hachana R, Berraies S, Ftiti Z. Identifying personality traits associated with entrepreneurial success; does gender matter?. *J Innovat Econ Manag.* 2018; 3(27): 169-93. doi: 10.3917/jie/027.0169.

A web-based decision support system to support occupational therapy services in promoting active ageing

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ABSTRACT

Background: Dealing with the consequences of Thailand's ageing population is a significant challenge. The growing usage of Information and Communication Technology (ICT) has the potential to support healthy and active ageing.

Objective: This study aimed to develop a web-based Decision Support System (DSS) and evaluate its usability.

Materials and methods: Research and Development (R&D) was a study design. It was divided into two phases: the development of the web-based DSS and its usability.

Results: The web-based DSS was designed under the requirements of the users and comprised seven components: 1) the login page; 2) the main page; 3) the register page; 4) active ageing measurement; 5) decision-making for older people; 6) the Occupational Therapy (OT) recommendations system; and 7) exporting information. A System Usability Score (SUS) of 80.41 in the usability test showed that the web-based DSS was very user-friendly and had excellent efficacy, efficiency, and satisfaction.

Conclusion: The web-based DSS effectively enhanced ageing for older people.

Introduction

The world's population is ageing rapidly. The active ageing framework of the World Health Organization (WHO)¹ has been adapted as a global strategy in ageing policies, practices, and research to respond to the ageing population. It emphasizes the connections between good health, participation, and security of older people's lives. Thailand has become a wholly aged society since 2023, when at least 20% of the population is 60 years or older.² Health promotion to promote a healthy life and encourage active ageing in older individuals can be an effective strategy to reduce the cost of care.³ The active ageing policy should be adopted and modified according to each country as the government's key. Thus, the Thai government adopted the original three components of WHO into four main components: health, social participation, security, and an enabling environment. These complex and various components impact older individuals' participation in everyday occupations.⁴ It is crucial to find solutions for various ageing concerns so that older people can maintain independence and lead healthy lives.

OT services address all aspects of ageing, from wellness strategies to rehabilitation.⁵ The effectiveness of health promotion within the scope of occupational therapy

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improves occupational performance and quality of life and decreases health care utilization for community-dwelling.⁶ The current trend in healthcare and health profession education is the increasing use of ICT to promote various health behaviors.⁷ ICT may be a key enabler for digital tools supporting the health and social care sectors. Improved quality of life, health, and well-being can help to prevent or delay frailty concerns.⁸ The profession of occupational therapy uses a wide range of ICTs,⁹ including advanced technologies such as robotics, artificial intelligence (AI), the Internet of Things (IoT), three-dimensional printing, virtual reality, and autonomous vehicles. Additionally, adaptive equipment, electronic wheelchairs, splints, and lifelike prosthetics are employed to assist clients in achieving independent living.¹⁰⁻¹³

Occupational therapists use theoretical conceptual practice frameworks to guide intervention decision-making and direct their thinking in occupational therapy practice. In practice, conceptual frameworks are the core concepts of occupational therapy thinking. They are not only to guide therapists in conducting the assessment but also to help them make better intervention decisions. The Person-Environment-Occupation (PEO) model is a valuable practice for all age groups. It focuses on the client's environment and occupation, which impact the performance of everyday occupations.¹⁴ This model identifies the interaction between people, environment, and occupation. People engage in occupations throughout their lives, such as activities, tasks, and roles. The connection between people, environment, and occupation helps to understand the quality of occupational performance (i.e., function), which results in the intersection of each component of the PEO model.¹⁵ Therefore, this model is efficient and comprehensive for application in research, as it encompasses a wide range of factors that impact individuals. Moreover, it is also related to the WHO's Active Aging, which focuses on older people's abilities to participate in social activities involving the active engagement of older people. Active aging is not new for OT, but OT practitioners should adopt and implement it more effectively.¹⁶ However, since most of the OT role primarily focuses on disability or rehabilitation, there is still a need to emphasize health promotion among older people. The challenges of OT services include adopting a new

approach to provide OT services for the ageing population. The challenges of OT services involve adopting a new approach to provide OT services for the ageing population. The development of the DSS in medical science has the potential to help clinicians and occupational therapists make decisions when choosing the most appropriate intervention.¹⁷ Furthermore, developing the DSS for OT service was to evaluate the clients' eye-hand coordination. The system was designed to reduce the burden and cost of having a qualified expert present at any evaluation or training session.

Occupational therapists and other healthcare providers develop the DSS to evaluate and determine the most appropriate intervention. In Israel, the DSS not only helped occupational therapists with their service delivery but also made it easier for architects, accessibility specialists, and rehabilitation professionals to evaluate facility accessibility.¹⁸ The DSS, a computerized audit tool, was created by combining an information system and decision support to investigate and analyze the accessibility of services for older people and people with disabilities. It significantly impacts clinicians and occupational therapists because it improves the overall outcome for their clients.²¹⁻²⁵ This study utilizes the DSS to improve service delivery and promote healthy lifestyles to enhance successful ageing among older people.

This study aimed to develop the web-based DSS as a novel solution to promote health and wellness for older people by combining the active ageing concept and the OT concept.

Materials and methods

This study was Research and Development (R&D). The web-based DSS was based on the active ageing concept. It consisted of two phases. The first phase was to develop the web-based DSS. The second phase was to evaluate the usability of the web-based DSS for promoting active ageing. Each phase of the study is described in detail as follows:

Phase I: The development of the web-based DSS.

Four stages were involved in developing the web-based DSS (Figure 1).

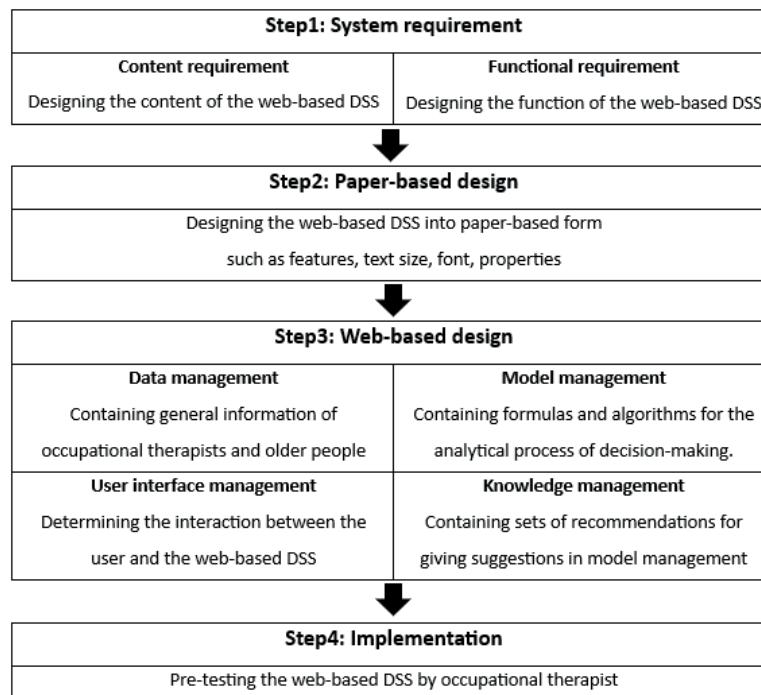


Figure 1. The developmental process of the web-based DSS.

Step 1: System requirement

The first phase of DSS development was formulating the system requirements. The researcher determined a list of user requirements to analyze and design the web-based DSS, including a working system or conditions that the user requires. Formulating the system requirements for the web-based DSS involved determining both the content requirements and the functional requirements.

Step 2: Paper-based design

During this phase, the researcher developed a paper-based decision support system (DSS) that complies with

the users' functional and content specifications. The paper-based design followed the user-centered interaction design.²⁶

Step 3: Web-based design

Software engineers are responsible for designing and developing web-based DSS under the specifications of the paper-based version of DSS. The system could be accessed through the Internet. Data management, model management, user interface management, and knowledge management are components of the framework of the web-based DSS (Figure 2).

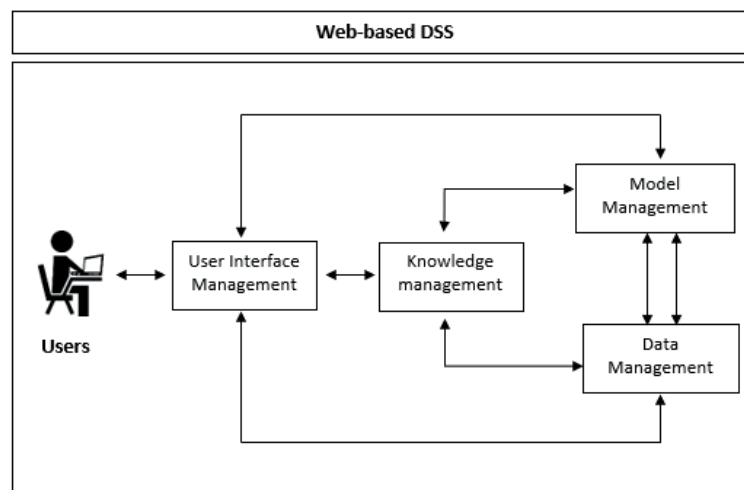


Figure 2. Conceptual view of the web-based DSS system.

Based on the active aging conceptual framework of the WHO was determined by studying components of the Active Ageing Index (AAI) indicator. It is a flexible tool that can apply the domains under the concept of active ageing to reflect the potential of older persons to the specific circumstances and purposes in their contexts. In Thailand, the National Institute on Ageing (NSO)²⁷ refined the initial formulation (health, participation, and security) further by adding a fourth component to enable an environment for active ageing as the fourth component. Therefore, the

researcher determined the indicators in four elements related to a paradigm shift for achieving active ageing in Thailand. Then, the PEO model was integrated into sets of recommendations (Figure 3).

We determined it by studying components of the AAI indicator, which is based on the WHO's active ageing conceptual framework. The AAI is a flexible tool that can apply the domains under the concept of active ageing, reflecting the potential of older persons to specific circumstances and purposes in their contexts.

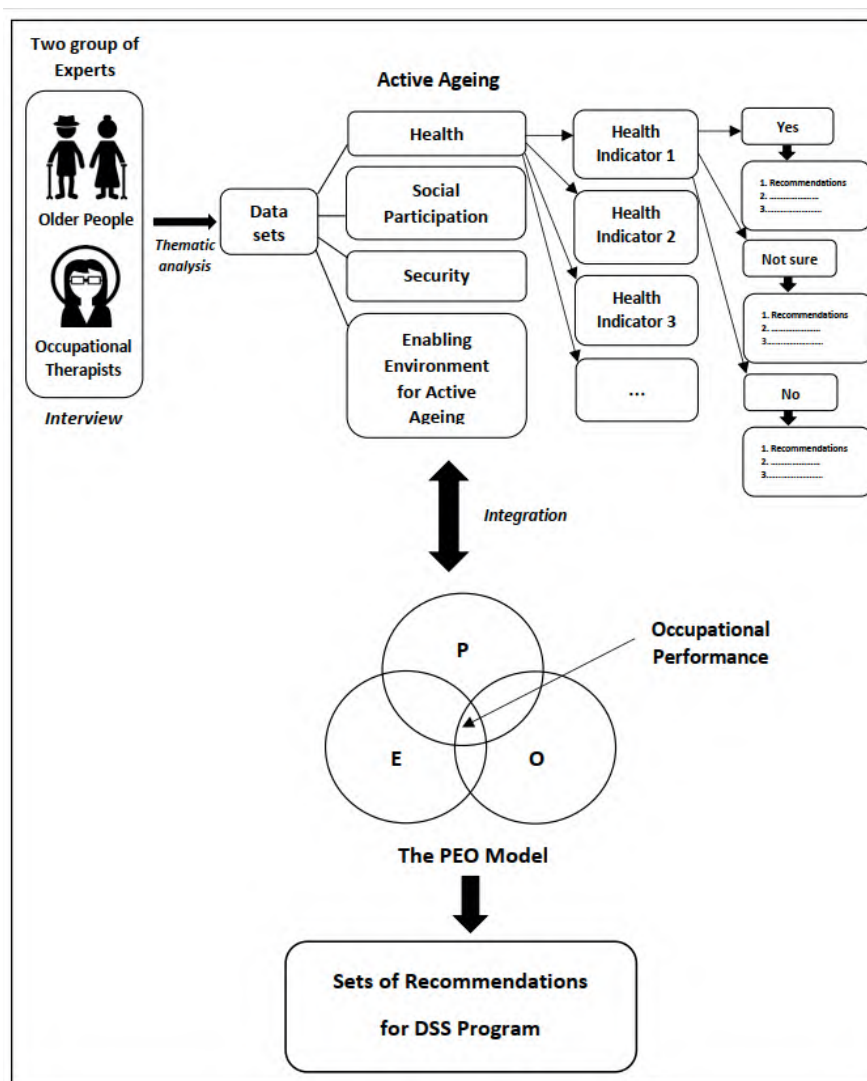


Figure 3. The development process of recommendations.

In this study, the AAI was measured using a previously developed measure.²⁸ The psychometric property achieved good internal consistency overall, as demonstrated by Cronbach's alpha of 0.77 and a test-retest reliability rating of 0.89, which led to the construction of a set of recommendations. It comprised 12 indicators and 25 questions about health, social participation, security, and an enabling environment for active ageing. The scoring system utilized three Likert scales to facilitate easy decision-making for older individuals. Each scale item has 3 categories: yes, not sure, and no, with scale values ranging from 1 to 3. The formula

for calculating each active ageing dimension follows Saengprachaksakula.²⁹ Each active ageing dimension (health, community participation, security, and enabling an environment) received a weighted score. After that, the AAI was categorized into three levels: low, moderate, and high, based on the Human Development Index of the United Nations Development Programme (UNDP).³⁰ Therefore, expert recommendations will be given for each possible response choice. We conducted in-depth interviews to extract tacit knowledge, adhering to the interview guideline that listed questions of active ageing measurement (12 indicators and 25 items). The experts

comprised 2 groups of 9 healthy older individuals aged 60 years and above who had demonstrated successful and healthy aging, as detailed below. absence of chronic disease and freedom from disability; participating in social activities at least once per month, such as being a member of a club or group, helping other people, or being a volunteer in the community; representing elite Thai older people who are accepted in society,³¹ and 8 occupational therapists who have practical experience in the senior field or have worked in the geriatric field for five years or more. The researcher used a note-taker and voice recorder to record the interview. Each interview session with the key informants ranged from 30 to 45 minutes. The researcher ensured the strict confidentiality of the interview data. The researcher acknowledged the confidentiality of the interview data and proceeded with the recording of the data. The data gathered from the interview were checked for credibility by using the review triangulation technique. After that, they were analyzed and interpreted by using thematic analysis.^{32,33} After conducting a thematic analysis, the researcher used the PEO model to incorporate the data into the OT framework. Subsequently, sets of recommendations were examined for their content validity using the IOC.

This evaluation of recommendation content was checked by 5 experts, who were occupational therapists and had 5 years or more practical experience in the geriatric field. Five experts, each with at least 5 years of practical experience in geriatrics, thoroughly examined the contents of the recommendations. Afterward, the researcher adjusted by following the experts' suggestions and comments. At last, the final version of the recommendations was completed. After formulating the recommendations, the DSS was constructed, and its implementation was carried out.

Step 4: Implementation.

Pre-testing the web-based DSS was part of this method. Five subjects participated in this step. The participants were selected using purposive sampling, following 2 criteria: they had to be occupational therapists with a minimum of 5 years of experience in working with the elderly, and they were not involved in the system development process of this study. The web-based DSS demonstrated how to use it for 20 minutes and then allowed occupational therapists to use it independently. One OT was evaluated on this system using one older individual as the subject. Subsequently, feedback regarding the system's features and functionalities was gathered. The engineering team improved the web-based DSS system based on user suggestions for usability issues, limitations, or additional aspects. Five occupational therapists tested the upgraded version of the web-based DSS system again to confirm its readiness for use, marking the completion of its final version.

Phase II: Testing the usability of the web-based DSS

To evaluate the readiness and compliance of the web-based DSS with user requirements and expectations.

According to Nielsen's recommendation for usability testing, a minimum of 20 users qualifies as statistically significant to identify usability defects with the product.³⁴ Consequently, the study's sample comprised 30 occupational therapists. The study used purposive sampling to select OTs who met the following criteria: having at least five years of professional experience working with geriatrics and not participating in this study's system development process. Each OT used the web-based DSS for 10 clients. There were 300 clients in total. Subsequently, the OTs evaluated usability using the SUS questionnaire. The researcher presented a demonstration of how to use the DSS system. The participants then spent a week testing the system with older people. The SUS was used to evaluate the system's usability, which covered three facets such as effectiveness (the ability of the user to complete the relevant tasks with output quality), efficiency (the level of resources used for performing the tasks), and satisfaction (subjective reaction to using the system from the users). The SUS comprises a 10-item scale rated on a 5-point Likert scale: 1 = strongly disagree, 2 = somewhat disagree, 3 = neither agree nor disagree, 4 = somewhat agree, and 5 = strongly agree. The SUS score calculation converted all 10 items' values into a range of 0 to 4. Subtract the score from 5 (5-X) for items 2, 4, 6, 8, and 10, and subtract 1 from the score (X-1) for items 1, 3, 5, 7, and 9. The scores from even and odd-numbered questions were summed up. We then multiplied the total scores by 2.5 to scale the result from 0 to 100. Scores above 70 were "very good," and scores below 50 were "very weak." The data from the system usability questionnaires was summarized to adjust the system with software engineering, including suggestions and comments about problems of use, limitations, or other factors. Then, the data was analyzed using descriptive statistics such as frequency, percentage, mean, and standard score.

Results

The web-based DSS

The system requirement is comprised of content requirements and functional requirements. The content requirements of the web-based DSS proposed three parts: occupational therapist information, older people, and recommendations. The functional requirement for using the web-based DSS with clients is that the users must create their accounts and log in with their username and password for privacy and security.

In addition, the system can record clients' data, calculate the AAI, analyze the client's data according to the PEO model, and generate OT recommendations for active ageing. Lastly, a system could export summarized reports on paper by printing them or emailing them. In addition, they requested video tutorials on how to use the system.

We designed the paper-based DSS based on user perspectives and system requirements. Once we developed the contents and functions of the web-based DSS, we logically mapped the flow chart of the web-based DSS process, as shown in Figure 4.

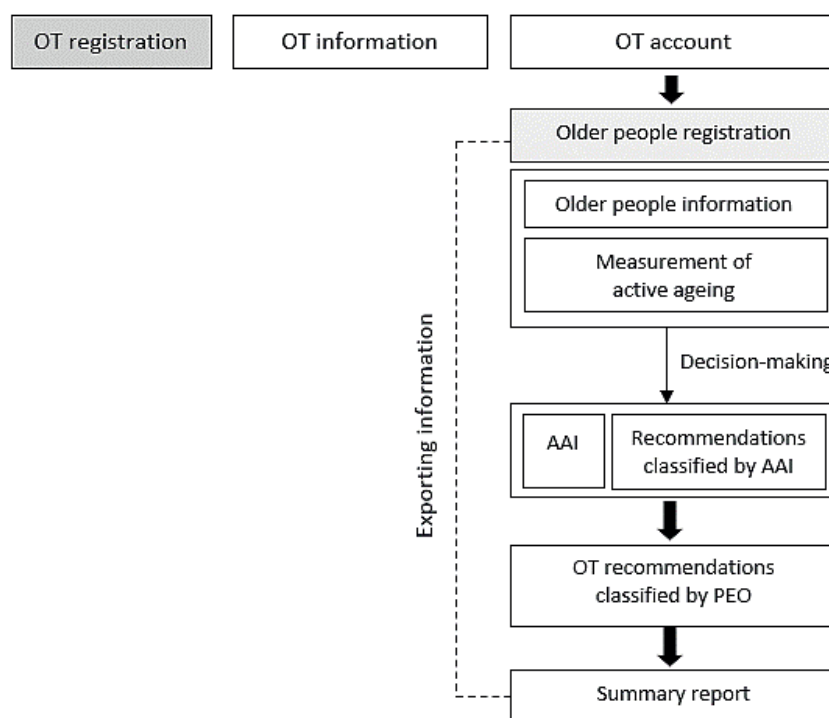


Figure 4. Logical connection of the web-based DSS.

The OT recommendations system comprises seven functional design components, including the login page, main page, register page, active ageing measurement, decision-making for older people, OT recommendations system, and information exporting. Then, the paper-based design was drafted to develop the web-based DSS by software engineering. The next step involved converting the paper-based DSS into a web-based version. Software engineer designed the web-based DSS and operated its features and functions. The system operated on the cloud, delivering Decision Support (DS) logic through a web browser to a computer, smartphone, or tablet through the Internet. The structure of the web-based DSS developed in this study consisted of 4 components: data, model, user interface, and knowledge management. The data management component consisted of a database, Database Management Subsystem (DBMS), query facility, and data directory. The database contained data from 2 sources: internal system data (OT suggestions) and external user data (occupational therapists and older people information). The DBMS formed a section for creating, accessing, and updating the database. Regarding the query facility, this section measured data accuracy and

validity. The data directory contained all the data in the database, which provided the information needed by the users.

The operational model management building process involved adding sets of recommendations to form a suggestion system model. The if-then rules were used for the analytical method of decision-making problems. The recommendations were designed based on individual active ageing levels, high, moderate, and low, and issues related to PEO model components. Then, to build a user interface style of the web-based DSS, 3 types were developed for this study: menu interface, point-and-click graphical interface, and question-and-answer interface. The user interface was completed to control interactions with computerized information systems. The final step involved offering suitable recommendations and using knowledge management to address issues. The older people's information and the summary of active ageing levels were encoded as if-then rules, and the sets of recommendations were represented to match active ageing levels and the problems of older people. The final web-based DSS system was divided into seven parts, as shown in Table 1.

Table 1. The DSS system to support occupational therapy services in promoting active aging.

DSS system	Specification
1. Login page	The first page appears for the user. For the first access, the user (OT) needs to log in by filling in the username and password. New users must create a new account to keep security of data collection.
2. Main page	This page will appear when the user logs in. There are two parts: log in and a video tutorial.
3. Register page	The purpose of the registration page is to allow OT to sign up new clients. Personal information can fill in such as name, age, gender, etc. When the personal information of each older person is filled out completely, the name of the client will appear on the registration information menu. On the registration information menu, users can view and edit individual information by clicking on the list.
4. Active ageing measurement	In this section are questions to measure the active ageing level of older people. One question at a time from each page will show until all 25 questions are answered.
5. Decision-making for older people	This section gives the overall results of the interpretation of the AAI and the brief description. Data is processed so that recommendations are chosen based on information that has already been received.
6. OT recommendations system	The integration between the PEO model and the active ageing of WHO is displayed by the recommendation system under the logical if-then. It consisted of a summary of information on older people and OT recommendations.
7. Exporting information	Three options are available to users for exporting the data. 1) an overview of older people information and specific suggestions for older people 2) the summarized list of recommendations under the PEO component, 3) the details of recommendations.

5 occupational therapists implemented the web-based DSS with older people to pre-test the system. After trialing the web-based DSS, users gave feedback on its contents and functions. For instance, the OT recommendation system suggested enlarging font and image sizes and altering the font's color. The final web-based DSS was completed.

Usability of the web-based DSS

A total number of 30 occupational therapists participated in the tests, of which the majority were female (66.67%) and aged about 30-40 years. Most of them worked at the practitioner level (66.67%) and had experience in geriatrics for five years or more, as shown in Table 2.

Table 2. Characteristics of the participants.

Variables	Frequency (N=30)	Percent (%)
Gender		
Male	10	33.33
Female	20	66.67
Age (yrs)		
25-30	7	23.33
30-40	21	70.00
>40	2	6.67
Category of Position		
Professional Level	4	13.33
Practitioner Level	20	66.67
Government Employees	1	3.33
Permanent Employees	3	10.00
Temporary Employees	2	6.67
Work experience (yrs)		
5-10	21	70.00
>10	9	30.00

The SUS score of the DSS was 80.41 (SD = 8.76), which indicated excellent usability.³⁵ The median rating of partially agree was provided for the positively worded SUS question “I thought the system was easy to use” because the median rating was 4.5, which could not be rated as agree. Therefore, a median rating of “strongly

disagree” was not found in this study. The median rating of partially disagree was provided for the negatively worded SUS question, “I thought that I would need the support of a technical person to be able to use this system,” the median rating was 1.5 and could not rate as disagree. The responses to SUS questions are shown in Table 3.

Table 3. Responses to SUS questions.

Question*	Median	±SD	SUS scores ±SD
1. I thought that I would like to use this system frequently	4	4.13±0.73	80.41±8.76
2. I found the system unnecessarily complex	2	2.16±0.75	
3. I thought the system was easy to use	4.5	4.4±0.67	
4. I thought that I would need the support of a technical person to be able to use this system	1.5	1.5±0.50	
5. I found that the various functions in this system were well integrated	4	4.30±0.47	
6. I thought there was too much inconsistency in this system	2	1.70±0.75	
7. I would imagine that most people would learn to use this system very quickly	4	4.27±0.52	
8. I found the system very cumbersome to use	2	1.60±0.62	
9. I felt very confident using this system	4	4.13±0.59	
10. I needed to learn a lot of things before I could get going with this system	2	2.13±0.81	

Note: 5=strongly agree, 4=agree, 3=neutral, 2=disagree, 1=strongly disagree, *questions 2, 4, 6, 8, and 10 are negative, the scores must be inverted before computing the SUS.

Discussion

The web-based DSS was developed as a tool to support OT services for older people. It is an innovation that can calculate the active ageing level before making decisions in selecting the recommendations, according to information on older people and their level of active ageing. The web-based DSS provides customized support for each client. OT can fill data into the program and then offer recommendations that arise from the integration of the OT concept (PEO) and the active ageing of the WHO framework. This study is growing as the focus shifts from rehabilitation to health promotion, and it has been recognized that there is an opportunity to offer additional services in this area.³⁷ Occupational therapists need to embrace the concept of occupation for health to adjust their approach towards promoting active ageing. Technology has become increasingly popular in occupational therapy, particularly concerning active ageing and its impact on the mental well-being of older individuals.³⁸ Although technology has improved convenience in life, there is still a lack of research on how to use new technologies to improve the health of older people. This study draws inspiration from the global strategy for digital health, which aims to integrate technology into occupational therapy practices to improve health and promote active ageing among older people. Zaalen et al.³⁹ mentioned that implementing technology in healthcare delivery to older people is an essential key factor in helping healthcare providers supply services efficiently to their clients.

The results of this study indicate that a web-based DSS to enhance active ageing is readily available for use.

Evaluation of the effectiveness of web-based DSS on the web is very challenging. According to previous research, web-based DSSs are helpful tools that give users various options for improving clinical practice.^{40,41} It was used to analyze data and then provide feedback to the users to assist them in solving problems and making decisions.⁴² This study developed a web-based DSS as an innovative approach to enhance the health and well-being of older individuals. The web-based DSS integrates the principles of active ageing and occupational therapy. The process is comparable to creating multi-domain solutions that aid in identifying deterioration in different domains early.⁴³ In this research, we implemented the web-based DSS to measure older people's activity levels and provide precise advice. The development of the web-based DSS followed the emergence of technology in occupational therapy, which enables occupational therapists to create new ways of assessing and providing intervention services for their clients.⁷

In occupational therapy research studies, the web-based DSS has been used as an expert to select, recommend, evaluate, and guide appropriate solutions for clients. For instance, the web-based DSS plays a crucial role in the process of choosing and prescribing assistive technologies,^{19,20} in the evaluation of the functional capabilities of the disabled user and selecting an appropriate combination of assistive devices,²² and in the assessment of access to facilities by architects, accessibility experts, occupational therapists, and rehabilitation experts.¹⁸ Therefore, this study used the web-based DSS as an occupational therapy tool to effectively serve older

people, providing them with specific recommendations in health promotion rather than rehabilitation. Furthermore, it was a cutting-edge piece of equipment that helped occupational therapists effectively serve their clients in occupational therapy.

In this study, we used the systems development life cycle (SDLC) to develop the web-based DSS, tailoring it to the user's needs, including system and usability requirements. In information systems development, we use SDLC to create applications and programming that align with user requirements.⁴⁴ The system requirement was the first step of system development and was used to determine a list of user needs for analyzing and designing the DSS.⁴⁵ The requirements in this study were developed from the perspective of occupational therapists, who were interviewed as users about the system's requirements for developing its content and functionality. The Sagel study demonstrated the importance of identifying user requirements.⁴⁶ Therefore, users identified a set of functions and capabilities to meet their needs. After determining the system requirement, the system was designed in paper-based form. This step defined the system's functions and features and the relationships among its components according to the system requirement. Paper prototyping proved to be an effective tool for exploring design possibilities while developing the system. It also served as a core activity in the design process, providing screenshots that aid in determining how the design or product should appear. The paper-based design of the system provided a low-cost prototype. An example of application development for hearing aids demonstrates how the initial paper-based prototype of this app contributed to its improvement.⁴⁷ In addition, Liu *et al.* created paper-based electronic interfaces for use in a watery environment, offering a simple and efficient way to create customized digital prototypes.⁴⁸ Following the paper-based design, the system development process adhered to the requirements and design phases. In this study, the cloud-hosted the web-based DSS, and a web browser delivered the DS logic to a computer, smartphone, or tablet through the Internet. In this study, the web-based DSS structure consisted of four components: data, model, user interface, and knowledge management, similar to the study by Oz.⁴¹ The sets of recommendations are based on the knowledge and experience of experts, specifically occupational therapists and older individuals with high levels of active aging. They are prepared for practical application in the real world. The database integrates other sources, such as academic literature and research, to enhance a comprehensive set of recommendations. The four components worked in conjunction to provide recommendations from occupational therapists to older people. As users, the occupational therapists completed older people's profiles, including their information. The occupational therapists then evaluated the older people for active ageing and processed and collected their active aging levels for data management. We used the if-then rules to assess the active ageing of older people at three levels. The web-based DSS provided appropriate

recommendations tailored to the active ageing level of older individuals. Therefore, the web-based DSS could be considered the intelligence system utilized to support and enhance decision-making activities. The web-based DSS was developed and designed based on user requirements to meet user needs better. However, before being used in clinical practice, the DSS must be evaluated to ensure its validity and efficiency.⁴⁹

The final web-based DSS was installed to give recommendations to older people. It was similar to that in a previous study by Palumbo *et al.*, which used qualitative methods to obtain a voluntary self-report from users who used the system provided.⁴¹ The interaction between the user and technology in this study was significant for supporting web-based DSS implementation.⁵¹ The usability of the DSS system during the testing phase in this study was evaluated to ensure that users could operate it efficiently. The outcome gave the user a clue about the crucial aspects they must consider before approval or rejection. This study selected The SUS for usability testing because it is utilized frequently. It is an often-used questionnaire that measures usability.⁵² This helpful tool is available in paper-based and online forms. It found excellent results (the SUS score was 80.41). It was explained that SUS above 80.3 represented excellent usability.⁵³ Therefore, usability testing helps developers determine whether the system's development aligns with user needs, indicating the system's success and user acceptance.

The result of usability testing reflects how the users felt about the web-based DSS, its effectiveness and efficiency, and whether they were satisfied. Regarding the degree of consistency in the system, the highest score in the SUS questionnaire was for Item 3 (Mean=4.4, SD=0.67). Users stated that they did not need the support of a technical person to use the system (Item 4: Mean=1.5, SD=0.50). Most question items required the users to answer before progressing to the next section. If an item of information was not entered, a reminder was displayed, following the principle of constraints and feedback, to help the user understand the process.⁵⁴ Consistency and simplicity in using the DSS were also expressed in items relating to the ease of learning the system; in Item 7 ($\bar{X}$ =4.27, SD=0.52), users indicated that they could learn to use the system very quickly. In Item 5 ($\bar{X}$ =4.30, SD=0.47), they stated that the various functions in this system were well integrated. In addition, in Item 2 ($\bar{X}$ =2.16, SD=0.75), the users stated that the system was unnecessarily complex. In Item 10, they said that operating the system did not require much prerequisite knowledge or preparation and indicated that it was easy for novice users to learn about its use. All SUS reflections showed that users had a satisfactory experience using the web-based DSS tool. The functionality and features of the web-based DSS were designed and developed with a focus on matching reliability and validity with the needs of the users. Therefore, the web-based DSS was created to meet user needs and make decisions to provide services effectively for older people.

Limitations and suggestions

This study has some limitations. The maintenance step requires continuous operation to meet the users' needs. Additionally, the post-implementation review used the maintenance process to monitor, evaluate, and modify the system as needed. However, the web-based DSS was designed for occupational therapists who are users to provide services for older people. Therefore, we limited the target users to only occupational therapists. The web-based DSS is a tool for occupational therapists to offer recommendations for older people.

Moreover, the system allows for the import of recommendations that meet the needs of specific older people in various formats, such as email and printing. Occupational therapists must consider and select a suitable form for older people, as some of them have limitations, particularly those who are illiterate. To maximize the benefits of the recommendations, the therapist may need to give guidance to family members who can help older people maintain a high quality of life and active ageing. Furthermore, the recommendations extracted knowledge from expert experiences. Therefore, these recommendations were representative of expert suggestions that were integrated through comprehensive knowledge.

Conflict of interest

The authors declared no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

Ethics approval

The Faculty of Associate Medical Sciences Ethics Committee, Chiang Mai University, approved this study (number: AMSEC63EX040).

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Supplementary data link

<https://dss.ot-localhealth.com/>. The web-based Decision Support System (DSS) is accessible through this link. After creating a new account, the new user can use a web-based system.

References

- [1] World Health Organization. Active ageing: a policy framework. Geneva, Switzerland: World Health Organization; 2002.
- [2] Foundation of Thai Gerontology Research and Development Institute. The situation of the Thai older people reports. Bangkok: TGRD; 2021.
- [3] National Statistical Office of Thailand. Active ageing index of Thai elderly. Bangkok: Text and general publication; 2017.
- [4] De Coninck L, et al. Promoting meaningful activities by occupational therapy in older people care in Belgium: the ProMOTe intervention. BMC Geriatr [Internet]. 2024; 275. Available from: <https://doi.org/10.1186/s12877-024-04797-6>.
- [5] Atwal A, McIntyre A. Occupational therapy and older people. 2nd Ed. Oxford, UK: Blackwell; 2005.
- [6] Berger S, Escher A, Mengle E, Sullivan N. Effectiveness of health promotion, management, and maintenance interventions within the scope of occupational therapy for community-dwelling older adults: a systematic review. Am J Occup Ther. 2018 Jul/Aug; 72(4): 7204190010p1-7204190010p10. doi:10.5014/ajot.2018.030346. PMID: 29953825.
- [7] Naidoo D, Govender P, Stead M, Mohangi U, Zulu F, Mbele M. Occupational therapy students' use of social media for professional practice. Afr J Health Prof Educ. 2018; 10(2): 101-5.
- [8] Liu L. Occupational therapy in the fourth industrial revolution. Can J Occup Ther. 2018; 85(4): 272-85.
- [9] Díaz D, Yee N, Daum C, Stroulia E, Liu L. Activity classification in independent living environment with JINS MEME eyewear. Proceedings of 2018 IEEE International Conference on Pervasive Computing and Communications, Athens. 2018: 1-9. doi: 10.1109/PERCOM.2018.8444580.
- [10] Lersilp S, Putthinoi S, Lertrakarnnon P, Silsupadol P. Development and usability testing of an emergency alert device for older people and people with disabilities. Sci World J. 2020: 1-7. doi.org/ 10.1155/2020/ 510 2849.
- [11] Yeh Y, Hou. T, Chang W. An intelligent model for the classification of children's occupational therapy problems. Expert Syst Appl. 2012; 39(5): 5233-42.
- [12] Hayes L. How technology usage is altering the Field of occupational therapy. Honors Projects, Grand Valley State University; 2012
- [13] Jao CS, Hier DB. Clinical decision support systems: an effective pathway to reduce medical errors and improve patient safety. In: Jao CS, editors. Decision Support Systems. London: InTech Europe; 2010.
- [14] Law M, Dunbar B., Person-Environment-Occupation Model, In Dunbar, B.D. (Ed), Occupational model for intervention with children and families (pp. 27-49). New Jersey: SLACK; 2007.
- [15] Law M, Cooper B, Strong S, Stewart D, Rigby P, Letts L. The Person-Environment-Occupation model: a transactive approach to occupational performance. Can J Occup Ther. 1996; 63(1): 9-12.
- [16] Clemson LM, Laver KE. Active ageing and occupational therapy align. Aust Occup Ther J. 2014; 61(3): 204-7.
- [17] Grantner JL, Gottipati R, Pernalet N, Fodor GA. Edwards S. Eye-hand coordination assessment/therapy, using a robotic haptic device. Proceedings of the IEEE 9th International Conference on Rehabilitation Robotics, Chicago. 2005: 25-28. doi: 10.1109/ICORR.2005.1501043.
- [18] Bendel J. (2006). Decision support system for evaluating accessibility of facilities. Isr Med J. 2006; 5(3): 1-17.
- [19] Danial-Saad A, Kuflik T, Weiss PL, Schreuer N. Effectiveness of a clinical decision support system for

- pointing device prescription. *Am J Occup Ther.* 2015; 69(2): 1-7.
- [20] Danial-Saad A, Kuflik T, Weiss PL, Schreuer N. Usability of clinical decision support system as a facilitator for learning the assistive technology adaptation process. *Disabil Rehabil: Assist Technol.* 2016; 11(3): 188-94.
- [21] Hosack B, Hall D, Paradice D, Courtney J. A look toward the future: decision support systems research is alive and well. *J Assoc Inf Syst.* 2012; 13(5): 315-40.
- [22] Chi C, Tseng L, Jang Y. Pruning a decision tree for selecting computer-related assistive devices for people with disabilities. *IEEE Trans Neural Syst Rehabil Eng.* 2012; 20(4): 564-73.
- [23] Hwang JE. Promoting healthy lifestyles with ageing: Development and validation of the health enhancement lifestyle profile (HELP) using the Rasch measurement model. *Am J Occup Ther.* 2010; 64: 786-95.
- [24] Johansson A, Björklund A. The impact of occupational therapy and lifestyle interventions on older persons' health, well-being, and occupational adaptation. *Scand J Occup Ther.* 2016; 23(3): 207-19. doi:10.3109/11038128.2015.1093544.
- [25] Kretzberg CB. Report of the LUCID framework: An introduction [Internet]. 2008 [cited 2023 April 20]. Available from: <http://courses.cs.vt.edu/~cs3724/spring99/notes/lucid-0.pdf>.
- [26] Nielsen J. How many test users in a usability study? [Internet]. 2012 [cited 2023 April 20]. Available from: <https://www.nngroup.com/articles/how-many-test-users/>.
- [27] National Institute on Ageing. Why population ageing matters: A global perspective [Internet]. 2007 [cited 2024 August 13]. Available from <https://www.nia.nih.gov/sites/default/files/2017-06/WPAM.pdf>.
- [28] Punyakaew A, Hsu HY, Lersilp S, Putthinoi S. Development and psychometric properties of a questionnaire to measure the active ageing index for older people. *J Assoc Med Sci.* 2023 Jan 1; 56(1): 150-8.
- [29] Saengprachaksakula S. The Determinants of Thai Active Ageing Level. *JSHRA.* 2014; 21(1): 139-67.
- [30] United Nations Development Programme (UNDP). Human development report 2005: International cooperation at a crossroads – aid, trade and security in an unequal world. New York, NY, USA: United Nations Development Programme; 2005.
- [31] Yodphet S. Active ageing attribution: A case study of elite Thai elderly (master's thesis). <http://cuir.car.chula.ac.th/bitstream/123456789/1970/3/Parichat.pdf>. [In Thai]; 2004.
- [32] Chantavanich S. Data analysis for qualitative research. Bangkok: Chulalongkorn University. [In Thai]; 2003.
- [33] Pothisita C. Data analysis for qualitative research. In C. Pothisita (Eds), *Qualitative Research* (pp. 360-361). Bangkok: Amarin. [In Thai]; 2006.
- [34] Alrooba R, Mayhew PJ. How many participants are really enough for usability studies. 2014 Science and Information Conference; 2014 August 27-29, London, UK; 2014.
- [35] Brooke J. SUS: a quick and dirty usability scale. In Jordan P.W, Thomas BC, Weerdmeester BA, McClelland AL. Editor. *Usability evaluation in industry* (pp. 189-94). London: Taylor and Francis; 1996.
- [36] Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Int J Hum Comput Stud.* 2008; 24(6): 574-94.
- [37] American Occupational Therapy Association. Report of occupational therapy's role with health promotion (AOTA Fact Sheet) [Internet]. 2014 [cited 2023 April 20]. Available from: https://www.aota.org/~media/Corporate/Files/AboutOT/Professionals/WhatIsOT/HW/Facts/FactSheet_HealthPromotion.pdf.
- [38] Coppola S. Occupation-centered practice with older adults with mental health conditions. *World Fed Occup Ther Bull.* 2011; 63(1): 5-8.
- [39] Zaalen Y, McDonnell M, Mikołajczyk B, Buttigieg S, Requena MC, Holtkamp F. Technology implementation in delivery of healthcare to older people: How can the least voiced in society be heard? [Internet]. *J Enabling Technol.* 2018; 12(2): 90. Available from: <https://doi.org/10.1108/JET-10-2017-0041>.
- [40] Dorr D, Bonner LM, Cohen AN, Shoai RS, Perrin R, Chaney E, Young AS. Informatics systems to promote improved care for chronic illness: a literature review. *J Am Med Inform Assoc.* 2007 Mar-Apr; 14(2): 156-63. doi: 10.1197/jamia.M2255.
- [41] Oz E. Management information systems. 5th Ed. Canada: Thomson Course Technology; 2006.
- [42] Kong D, Wang Y, Sun K. Design of care decision support system based on home-based behavior of elderly: a design science study [Internet]. *SAGE Open* 2022; 12(1). Available from: <https://doi.org/10.1177/2158240221086606>.
- [43] Orte S, et al. Dynamic decision support system for personalized coaching to support active ageing. *Artificial Intelligence for Ambient Assisted Living*; 2018 November 20-23; Trento, Italy; 2018.
- [44] Iam-siriwong O, Chueniam S. Management information system. Bangkok: SE-education; 2015.
- [45] Gunawardhana L. Process of requirement analysis link to software development. *J Softw Eng.* 2019; 12(10): 406-22. doi: 10.4236/jsea.2019.1210025.
- [46] Segal T. Decision support system-DSS [Internet]. 2019 [cited 2023 April 20]. Available from: <https://www.investopedia.com/terms/d/decision-support-system.asp>.
- [47] Wagner-Hartl V, Schmidtke B, Herbst T, Rudisile J, Mix L. Development of mHealth-Apps for Hearing Aids – Requirements and Assessments of a First Prototype. In: Stephanidis C, Antona M, Ntoa S, Salvendy G, editors. *HCI International 2022 – Late Breaking Posters*. HCII 2022. Communications in Computer and Information Science. Springer: Cham; 2022. P 1654. https://doi.org/10.1007/978-3-031-19679-9_59.
- [48] Liu L, et al. Design and Fabrication of Paper-Based Electronic Interfaces for the Water Environment [Internet]. *Electronics.* 2021; 10(5): 604. Available

- from: <https://doi.org/10.3390/electronics10050604>.
- [49] Meyer B. Seven principles of software testing. IEEE Computer. 2008; 41(10): 99-101.
- [50] Palumbo F, et al. "Hi This Is, NESTORE, Your Personal Assistant": design of an integrated IoT system for a personalized coach for healthy ageing. Front Digit Health. 2020; 2. doi:10.3389/fdgth.2020.545949.
- [51] Tokgöz P, Hafner J, Dockweiler C. Factors influencing the implementation of decision support systems for antibiotic prescription in hospitals: A systematic review. BMC Med Inform Decis Mak. 2023; 23(27). Available from: <https://doi.org/10.1186/s12911-023-02124-4>.
- [52] Hyzy M, Bond R, Mulvenna M, Bai L, Dix A, Leigh S, Hunt S. System usability scale benchmarking for digital health apps: meta-analysis. JMIR Mhealth Uhealth. 2022 Aug 18; 10(8): e37290. doi: 10.2196/37290.
- [53] Baber C, Haniff DJ, Woolley SI. Contrasting paradigms for the development of wearable computers. IBM Syst J. 1999; 38: 551-65.
- [54] Dillon A. Beyond usability: process, outcome and affect in human computer interactions. Can J Libr Infor Sci. 2002; 26: 57-69.

Psychometric properties of the self-report questionnaire on occupational balance in university students with game addiction

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ABSTRACT

Background: The prevalence of adolescents and young adults playing games on the internet is increasing worldwide. However, excessive game playing can cause game addiction among adolescents. Studies have demonstrated that game addiction increases the risks of physical and mental health problems, leading to occupational performance issues. Nevertheless, what level of game addiction impacts occupational health issues is controversial. Therefore, this study focused on occupational balance, an individual's perception of a proper amount and diversity of activities. The study demonstrated that occupational imbalance could lead to a decrease in an individual's occupational performance. However, an appropriate instrument for screening occupational balance in young adults with game addiction has never been studied yet, especially in a Thai version.

Objective: This study aimed to develop a self-report questionnaire on occupational balance for Thai university students with game addiction.

Materials and methods: The questionnaire consisted of 21 items divided into four dimensions, including the individual's perceptions of participating in meaningful activities, having the proper proportion of time to perform occupations, having the appropriate variety of professions, and being satisfied with their health and well-being. In addition, the psychometric properties of a questionnaire were investigated.

Results: The questionnaire had sufficient validity and good internal consistency for screening occupational balance in Thai university students with game addiction. The questionnaire was divided into four dimensions, each with good construct validity and internal consistency.

Conclusion: The questionnaire was valid and reliable for evaluating occupational balance for Thai university students with game addiction. This information can provide a new occupational therapy instrument for identifying occupational balance in the population with game addiction.

Introduction

Nowadays, the prevalence of adolescents and young adults playing games on the internet is increasing worldwide.¹ Subsequently, the studies indicated that excessive game playing can result in numerous physical and mental health problems,² including game addiction.³ This is consistent with evidence of game addiction increasing progressively in the adolescent and young adult population.⁴ In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the World Health Organization (WHO) reported that internet gaming disorder or game addiction is a mental health condition defined as a continuous and repetitive pattern of gaming behavior.³

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Studies have shown that game addiction can lead to various public health issues, including impaired emotional control, attention deficit, and cognitive dysfunction.^{5,6} They also concurred that game addiction among adolescents increases the risks of physical and mental health problems, thus leading to occupational performance issues such as poor sleep quality.⁷ This aligns with studies reporting that game addiction decreases the chance of interpersonal interactions and good school performance.^{8,9} However, the severity of game addiction's impact on occupational performance remains controversial. Some studies have suggested that game playing can be beneficial in various ways, such as increased relaxation, cognitive processing, and visual perception.^{10,11} Therefore, researchers are looking for suitable predictors to screen occupational performance issues in individuals with game addiction.

It is known that occupational balance is one of the critical concepts used in occupational therapy interventions. Studies have shown that occupational balance relates to an individual's occupational performance.^{12,13} It is consistent with a study that demonstrated that occupational imbalance increases the risk of stress-related disorders and leads to an individual's poor occupational performance.¹⁴ Therefore, this study focuses on the concept of occupational balance for screening occupational balance issues in Thai university students with game addiction. Currently, many occupational therapists define occupational balance as an individual's satisfaction with their health and well-being.¹⁵ Some studies suggested that occupational balance involves an equilibrium of self-care, leisure, play, work, education, and sleep.¹⁶ In contrast, others define it as an individual's perception of having a proper amount and variety of activities.¹⁷ This study proposed a new definition of occupational balance,^{15,17-19} which includes four dimensions: 1) participation in meaningful activities, 2) appropriate allocation of time to perform occupations, 3) having an appropriate variety of occupations, and 4) satisfaction with health and well-being.

Occupational therapists are developing instruments or questionnaires to assess an individual's occupational balance. For example, Dur *et al.*¹⁹ developed a self-reported occupational balance questionnaire focusing on patients' perspectives rather than those of occupational therapists.¹⁹ Moreover, Wagman and Håkansson developed the Occupational Balance Questionnaire (OBQ), emphasizing satisfaction with the number and variety of occupations.²⁰ However, an appropriate instrument for screening occupational balance in young adults with game addiction has not been studied, especially in a Thai context.

Thus, this study developed a self-report questionnaire on occupational balance for Thai university students with game addiction based on the new definition mentioned above. The psychometric properties in designing the questionnaire were also investigated in this population. It is hoped that this research will provide a new occupational therapy instrument to identify occupational balance in adolescents and young adults with game addiction.

Materials and methods

Participants

The participants in this study were undergraduate students from Chiang Mai University. The inclusion criteria were: (1) being an undergraduate student, (2) having no history of psychiatric disorders, and (3) having no physical disabilities. Ethics approval was granted by the ethics committee of the faculty of Associated Medical Sciences, Chiang Mai University (Ethic number: AMSEC-66EX-034). All participants provided written informed consent.

The sample size calculation was calculated using G*Power software 3.1.9.7 (effect size=0.4, power of test=0.8, alpha=0.05, a two-tailed test). In this study, 200 undergraduate students were divided into two groups of 100 individuals: one group with game addiction and the other without it, to test construct validity using the known group technique. Game addiction was assessed using the game addiction screening test for children and adolescents.²¹ Additionally, the sample size for measuring the reliability of internal consistency was calculated using Bonett's formula.²² A single coefficient of Cronbach's alpha test was used to calculate the sample size. According to Bonett's formula, the value of Cronbach's alpha at null hypothesis (CA0) and the expected value of Cronbach's alpha (CA1) could be any value ranging from -1 to 1. CA0 is more than zero if the researcher assumes a high internal consistency of the questionnaire items.²² Thus, this study set the values of CA0 and CA1 as 0.55 and 0.7, respectively. It is known that the good power of a test can be 0.8 or greater. Therefore, the power of the test was set at 0.8 in this study. Moreover, the number of items in the questionnaire (k) and the probability of type I error (alpha) were also set as 21 and 0.05, respectively. Finally, one hundred and three undergraduate students with game addiction were used to measure internal consistency reliability (CA0=0.55, CA1=0.7, alpha=0.05, and power of test=0.8, k=21).

Research design of this study

Phase 1: Development of the self-report questionnaire on occupational balance for university students with game addiction.

The self-report questionnaire, featuring five Likert rating scales, was developed based on the occupational science tenet. According to occupational science, engaging in meaningful activities enhances individuals' awareness of their abilities and self-worth.²³ However, such engagement in meaningful activities should be balanced across various aspects, including participation in diverse daily activities, appropriate allocation of time to perform each activity, and overall satisfaction with health and well-being.^{17,18} In addition, occupational balance considers the perspective of roles, which are unique and vary for each person.¹⁹ Therefore, the developed questionnaire in this study consisted of five Likert rating scales with items of question to evaluate individuals' perceptions in four dimensions. The five Likert rating scales measured levels of agreement for each item: 1 point = strongly disagree, 2 points = disagree, 3 points = neither agree nor disagree, 4 points =

agree, and 5 points = strongly agree.

Subsequently, the content validity of the questionnaire was evaluated by five experts: 1) a psychiatrist who has experienced working with children and adolescents with game addiction; 2) an occupational therapist specializing in occupational balance; 3) two occupational therapists experienced in treating individuals with mental health problems; and 4) an occupational therapist experienced in developing occupational therapy assessment tools. In this study, a psychiatrist is a validator of questionnaires looking into the behavior of game addiction, such as the amount of time and frequency of game playing. Occupational therapists experienced in treating individuals with mental health problems are the validators of questionnaires looking into the game addict's perception of participating in

meaningful activities as well as the impact of game addiction on occupations. An occupational therapist specializing in occupational balance validates questionnaires looking into the accuracy of all relevant aspects of occupational balance. Moreover, an occupational therapist experienced in developing occupational therapy assessment tools is a validator of questionnaires looking into the precision of occupational therapy assessment tools. After that, the developed questionnaire was adjusted following experts' recommendations and was tested in a pilot study with 12 college students with gaming addiction. Finally, the self-report questionnaire consisted of five Likert rating scales with 21 items to evaluate individuals' perceptions in the four dimensions above. Each item of the questionnaire is shown in Table 1.

Table 1. Items of the self-report questionnaire on occupational balance in university students with game addiction.

Items of the questionnaire	Questions
Dimension 1: Individual's perception of participating in meaningful activities	
1	Basic activities of daily living hold meaning and value for you.
2	Instrumental activities of daily living hold meaning and value for you.
3	Health management activities hold meaning and value for you.
4	Rest and sleep activity hold meaning and value for you.
5	Education holds meaning and value for you.
6	Work holds meaning and value for you.
7	Leisure activities hold meaning and value for you.
8	Social participation activities hold meaning and value for you.
Dimension 2: Individual's perception of having the proper amount of time to engage occupations	
9	Each day, you allocate an appropriate time for each activity.
10	The distribution of time among occupations each day is appropriate.
11	Despite playing game every day or almost every day, you can still effectively manage your time and daily activities.
Dimension 3: Individual's perception of having a suitable range of occupations	
12	Each day, you typically engage in a variety of activities.
13	Your daily activities contribute to a good quality of life.
14	You prefer to focus on activities that align with your role each day.
15	Engaging in a variety of activities brings you happiness.
16	Each week, you often make time for activities outside of your education or work commitments.
Dimension 4: Individual's perception of being satisfied with their health and well-being	
17	You are content with your physical health.
18	You are content with your mental health.
19	You are satisfied with your relationships with close individuals such as family, close friends, and partners.
20	You are satisfied with your relationships with others, such as colleagues and strangers.
21	You are satisfied with your physical environment where you engage in activities.

Phase 2: Study of psychometric properties of the questionnaire.

In this study, the questionnaire's psychometric properties, including content validity, construct validity, and reliability, were investigated. Five experts assessed Content validity using the index of item-objective congruence (IOC), while construct validity was examined using the known-group technique. Additionally, internal consistency reliability was investigated in young adults with game addiction.

Data analysis

An IOC value of 0.5 or higher was considered acceptable.²⁴ Construct validity was tested using the known-group technique and analyzed with an independent t-test.²⁵ If the average scores of the two groups (those with and without game addiction) were significantly different, the questionnaire was regarded to have good construct validity.²⁵ Internal consistency of the questionnaire was assessed using Cronbach's alpha.²⁶ A Cronbach's alpha value of 0.7 or higher indicated good internal consistency.²⁶

A two-sided p-value of 0.05 was considered significant for all statistical tests.

Results**Demographic data of the participants**

The demographic data of the participants are shown in Table 2. The results showed that the average age of the participants in the groups with and without game addiction was 19.70 ± 1.29 and 20.02 ± 1.21 , respectively. Regarding financial status, the average monthly income in the groups with and without game addiction was 8387.37 ± 5862.28 and 7730.39 ± 4926.78 Baht, respectively. Furthermore, the average monthly expense related to games in groups with and without game addiction was 532.81 ± 781.22 and 49.23 ± 115.26 Baht, respectively. For time spent playing games, the average game time per day and week in the group with game addiction was 106.12 ± 63.15 min and 5.44 ± 1.62 days, respectively, while the average game time per day and week in the group without game addiction was 80.21 ± 66.92 minutes and 3.53 ± 2.42 days, respectively.

Table 2. Demographic data of participants.

Variables	Group with game addiction (N=103)	Group without game addiction (N=103)
Gender		
Male (N, %)	34, 33.01%	42, 40.78%
Female (N, %)	69, 66.99%	61, 59.22%
Age average (years)	19.70 ± 1.29	20.02 ± 1.21
Academic year		
1 st year (N, %)	34, 33.01%	39, 37.86%
2 nd year (N, %)	20, 19.42%	30, 29.13 %
3 rd year (N, %)	46, 44.66%	20, 19.42%
4 th year (N, %)	1, 0.97%	13, 12.62%
>4 th year (N, %)	2, 1.94%	1, 0.97%
Financial status		
Average income/month (Baht)	8387.37 ± 5862.28	7730.39 ± 4926.78
Average expense related to game/ month (Baht)	532.81 ± 781.22	49.23 ± 115.26
Time spent game playing		
Average game time per day (min)	106.12 ± 63.15	80.21 ± 66.92
Average game time per week (days)	5.44 ± 1.62	3.53 ± 2.42

Content validity of the self-report questionnaire on occupational balance for young adults with game addiction

The content validity of the questionnaire was tested using the index of item objective congruence (IOC) by five experts. Based on their recommendations, the questionnaire was revised to include definitions and examples of technical terms for better clarity for respondents. Finally, the 21-item questionnaire was used to test content validity. The results showed high overall congruences (IOC=0.92), particularly on the following dimensions: 1) participation in meaningful activities (IOC=0.93), 2) proper allocation of time to perform occupations (IOC=0.95), 3) appropriate variety of occupations (IOC=0.88), and 4) satisfaction with health and well-being (IOC=0.96).

Construct validity of the self-report questionnaire on occupational balance for young adults with game addiction

The construct validity of the self-report questionnaire was assessed to determine its effectiveness in evaluating occupational balance (Table 3). This assessment was conducted using the known-group technique with an independent t-test analysis. This result suggested that the questionnaire had good construct validity. Furthermore, the questionnaire revealed significant differences between the groups in each dimension: dimension 1 ($p=0.001$); dimension 2 ($p=0.002$); dimension 3 ($p=0.001$); and dimension 4 ($p=0.003$) (Table 3).

Table 3. Construct validity of questionnaire.

Items of questionnaire	Group with game addiction (N=100) (Mean±SD)	Group without game addiction (N=100) (Mean±SD)	p value
Average score of total items of the questionnaire	78.59±9.02	86.26±8.91	0.000*
Average score of all items in dimension 1	34.33±3.69	35.87±3.03	0.001*
Average score of all items in dimension 2	9.38±3.60	11.33±2.76	0.000*
Average score of all items in dimension 3	16.48±5.92	19.24±3.27	0.000*
Average score of all items in dimension 4	18.40±3.71	19.82±3.01	0.003*

Note: * $p < 0.05$ indicates the statistically significant average questionnaire scores between groups with and without game addiction.

Dimensions 1 to 4 correspond to the individual's perceptions of participating in meaningful activities, having the proper amount of time to engage in occupations, having a suitable range of professions, and being satisfied with their health and well-being, respectively.

Reliability of the self-report questionnaire on occupational balance for young adults with game addiction

The sample used to investigate the internal consistency reliability was the same as the known-group technique cohort, explicitly focusing on individuals with game addiction. The test results using Cronbach's alpha coefficient indicated that all questionnaire items had a Cronbach's alpha coefficient of 0.83. Moreover, each dimension of the questionnaire demonstrated the following: dimension 1 (Cronbach's alpha=0.66), dimension 2 (Cronbach's alpha=0.71), dimension 3 (Cronbach's alpha=0.76), and dimension 4 (Cronbach's alpha=0.80).

Discussion

Some studies have shown that game playing has beneficial effects, such as enhancing cognitive function and promoting relaxation.^{10,11} However, excessive game playing can cause several public health problems, such as impaired emotional control, attention deficits, or cognitive dysfunction, leading to game addiction.^{5,6} Therefore, deciding what level of game addiction impacts occupational health issues is controversial. This study focused on occupational balance, defined as the equilibrium in performing daily occupations, such as self-care, education, work, leisure, and play.¹⁶ It is possible that excessive time spent on one activity, such as game playing, may cause loss of occupational balance and lead to occupational health issues. This is consistent with the definition of occupational imbalance, which is spending excessive time on one activity, leading to poor quality of life.¹⁸⁻²⁷ Additionally, studies have reported that occupational balance is related to individual occupational performance.^{12,13} It is known that occupational performance is an essential component for exploring occupational health issues.²⁸ Therefore, it seems likely that occupational imbalance caused by game addiction may lead to a deficit in occupational performance in game addicts and lead to poor quality of life. This is consistent with studies that demonstrate the effects of game addiction on performance and effectiveness in daily life activities such as sleep, education, and work achievement. Game addiction also affects participation in daily life activities of individuals through a loss of emotional control, attention deficit, and cognitive impairment.^{8,9,29-31} Therefore, the concept of occupational balance may be

used as a predictor of occupational health issues in game addicts via decreasing occupational performance in daily occupations and activities relevant to the role of the individual.

Occupational therapists are currently developing instruments or questionnaires to assess the occupational balance of an individual based on its definition. Many occupational therapists clarify the meaning of occupational balance differently, such as perspectives of an individual on participation in diverse daily activities, appropriate allocation of time spent in performing each activity, or satisfaction with health and well-being.^{17,18} However, there are no instruments or questionnaires for evaluating all definitions of occupational balance. For example, a self-reported occupational balance questionnaire focuses on the patient's perspectives rather than those of occupational therapists.¹⁹ In contrast, the Occupational Balance Questionnaire (OBQ) focuses on job satisfaction.²⁰ Therefore, the questionnaire in this study was developed based on a new definition that focuses not only on the appropriate amount of variety and time spent on daily activities but also on the importance of satisfaction with health and well-being and doing purposeful and meaningful activities. This study developed a Thai version of the instrument to screen occupational balance in individuals with game addiction, based on the new concept of occupational balance in four dimensions: participation in meaningful activities, appropriate allocation of time to perform occupations, having an appropriate variety of professions, and satisfaction with health and well-being. After that, the psychometric properties testing of the questionnaire was conducted. It was found that this study is the first to validate and establish reliability of such a questionnaire for Thai university students with game addiction. Moreover, the psychometric properties in each dimension of the questionnaire were tested, and the results were as follows.

In dimension 1, eight questionnaire items assess an individual's participation in meaningful activities. It has been known that occupational balance consists of both the temporal aspect and of the valued or meaningful occupations.¹⁸ The results of this study showed that dimension 1 of the questionnaire has good content and construct validity. This finding indicates that the questionnaire can accurately measure an individual's

perception of participating in meaningful activities. However, the internal consistency of items in dimension 1 was questionable (Cronbach's $\alpha=0.66$), indicating response variability. This variability may stem from differences in how individuals perceive participation in meaningful activity. Additionally, individuals may have distinct characteristics and daily occupational patterns that influence their lifestyle. For example, some individuals may find education significant, while others may not. Thus, the internal consistency value of items in dimension 1 reflected variation in responses.

In dimension 2, three questionnaire items assess the individual's perception of having a proper proportion of time to perform activities. It is consistent with a study that defined occupational balance as an individual's perception of adequate time spent on each activity.¹⁸ Another study demonstrated that game addiction is positively correlated with increased time spent playing games,³² which can subsequently lead to an inability to perform daily activities and result in occupational imbalance. The results of this study showed that the items in dimension 2 have acceptable levels of validity and reliability. Therefore, the questionnaire is suggested to be an effective tool for measuring occupational balance among Thais addicted to game playing, specifically in the dimension of having a proper proportion of time to perform occupations.

In dimension 3, five questionnaire items assess the individual's perception of having the appropriate variety of occupations. It is consistent with a study that reported that a variety of occupations is an important aspect of occupational balance.¹⁷ Furthermore, occupational balance emphasizes doing or engaging in a diverse range of occupations,¹⁷ related to health and well-being.³³ This study found that the validity and reliability of items in dimension 3 were acceptable. Therefore, the questionnaires are recommended as an effective tool for measuring occupational balance among Thais addicted to game playing, specifically regarding having the appropriate variety of occupations.

In dimension 4, five questionnaire items assess the individual's perception of satisfaction with health and well-being. It is established that health and well-being are closely related to occupational balance.¹⁸ The items in dimension 4 represent physical, mental, and social engagement satisfaction, aligning with the World Health Organization's definition of health and well-being.³⁴ This study's results indicated that the validity and reliability of items in dimension 4 were acceptable. Therefore, the questionnaire has the potential to effectively measure the satisfaction of Thais addicted to game playing with their health and well-being.

This study developed a new instrument for evaluating occupational balance, focusing on an individual's perception of performing daily activities in four dimensions, as mentioned above. Occupational balance is unique to each person and reflects their specific occupations and lifestyle performances. The value and meaning of professions may vary among individuals. This study demonstrated that the questionnaire has acceptable validity and reliability for

assessing occupational balance among Thai adolescents and young adults with game addiction. However, this study cannot test the exploratory factor analysis due to the limited sample size. In the future, the questionnaire needs to be tested to confirm the construct validity. Therefore, it suggested that the findings of this study can contribute to the development of new occupational therapy tools for identifying and addressing occupational balance issues in populations addicted to gaming. Moreover, it can serve as a valuable tool for exploring individual occupational concerns and for future planning of occupational therapy interventions for Thais addicted to game playing.

Conclusions

This pioneering study demonstrated that the self-report questionnaire exhibits acceptable validity and reliability in evaluating occupational balance among Thai adolescents and young adults with game addiction. These findings introduce a new occupational therapy instrument to identify occupational balance issues in such a population.

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Conflict of interest

The authors declare no conflict of interest.

References

- [1] Kim D, Lee J. Addictive Internet Gaming Usage among Korean Adolescents before and after the Outbreak of the COVID-19 Pandemic: A Comparison of the Latent Profiles in 2018 and 2020. *Int J Environ Res Public Health*. 2021; 18(14). doi: 10.3390/ijerph18147275
- [2] Basdas O, Ozbey H. Digital game addiction, obesity, and social anxiety among adolescents. *Arch Psychiatr Nurs*. 2020; 34(2): 17-20. doi: 10.1016/j.apnu.2019.12.010
- [3] Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry*. 2013; 12(2): 92-8. doi: 10.1002/wps.20050
- [4] Gao YX, Wang JY, Dong GH. The prevalence and possible risk factors of internet gaming disorder among adolescents and young adults: Systematic reviews and meta-analyses. *J Psychiatr Res*. 2022; 154: 35-43. doi: 10.1016/j.jpsychires.2022.06.049
- [5] Zhao W, Wei T, Zhou R, Wang Y, Wang Y, Ren Z, et al. The Influence of Online Game Behaviors on the Emotional State and Executive Function of College Students in China. *Front Psychiatry*. 2021; 12: 713364. doi: 10.3389/fpsy.2021.713364
- [6] Dong G, Li H, Wang L, Potenza MN. Cognitive control and reward/loss processing in Internet gaming disorder: Results from a comparison with recreational Internet game-users. *Eur Psychiatry*. 2017; 44: 30-8. doi: 10.1016/j.eurpsy.2017.03.004

- [7] Alghamdi FAD, Alghamdi FAG, Abusulaiman A, Alsulami AJ, Bamotref M, Alosaimi A, et al. Video Game Addiction and its Relationship with Sleep Quality among Medical Students. *J Epidemiol Glob Health*. 2024; 19: 1-8. doi: 10.1007/s44197-024-00265-x
- [8] Yang SY, Wang YC, Lee YC, Lin YL, Hsieh PL, Lin PH. Does Smartphone Addiction, Social Media Addiction, and/or Internet Game Addiction Affect Adolescents' Interpersonal Interactions? *Healthcare*. 2022; 23:10: 963-77. doi: 10.3390/healthcare10050963
- [9] Van den Eijnden R, Koning I, Doornwaard S, van Gurp F, Ter Bogt T. The impact of heavy and disordered use of games and social media on adolescents' psychological, social, and school functioning. *J Behav Addict*. 2018; 7(3): 697-706. doi: 10.1556/2006.7.2018.65
- [10] Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. Brains on video games. *Nat Rev Neurosci*. 2011; 12(12): 763-8. doi: 10.1038/nrn3135
- [11] Feng J, Spence I, Pratt J. Playing an action video game reduces gender differences in spatial cognition. *Psychol Sci*. 2007; 18(10): 850-5. doi: 10.1111/j.1467-9280.2007.01990.x
- [12] Martin Perez AM, Maximo-Bocanegra N, Rivas Ruiz F, Alguacil-Diego IM, Martinez-Piedrola RM. [Occupational balance, disability and functionality in people with rheumatic disease]. *An Sist Sanit Navar*. 2023; 46(3): e1053-62. doi: 10.23938/ASSN.1053
- [13] Magnusson L, Hakansson C, Brandt S, Oberg M, Orban K. Occupational balance and sleep among women. *Scand J Occup Ther*. 2021; 28(8): 643-51. doi: 10.1080/11038128.2020.1721558
- [14] Hakansson C, Ahlborg G, Jr. Occupational imbalance and the role of perceived stress in predicting stress-related disorders. *Scand J Occup Ther*. 2018; 25(4): 278-87. doi: 10.1080/11038128.2017.1298666
- [15] AA. W. An occupational perspective of health. 2nd ed. ed: Thorofare, NJ: Slack.; 2006.
- [16] Nurit W, Michal AB. Rest: a qualitative exploration of the phenomenon. *Occup Ther Int*. 2003; 10(4): 227-38. doi: 10.1002/oti.187
- [17] Wagman P, Hakansson C, Bjorklund A. Occupational balance as used in occupational therapy: a concept analysis. *Scand J Occup Ther*. 2012; 19(4): 322-7. doi: 10.3109/11038128.2011.596219
- [18] Backman CL. Occupational balance: exploring the relationships among daily occupations and their influence on well-being. *Can J Occup Ther*. 2004; 71(4): 202-9. doi: 10.1177/000841740407100404
- [19] Dur M, Steiner G, Fialka-Moser V, Kautzky-Willer A, Dejaco C, Proding B, et al. Development of a new occupational balance-questionnaire: incorporating the perspectives of patients and healthy people in the design of a self-reported occupational balance outcome instrument. *Health Qual Life Outcomes*. 2014; 12: 45. doi: 10.1186/1477-7525-12-45
- [20] Wagman P, Hakansson C. Introducing the Occupational Balance Questionnaire (OBQ). *Scand J Occup Ther*. 2014; 21(3): 227-31. doi: 10.3109/11038128.2014.900571
- [21] Pornnoppadol P. SB, Khamklieng K., Pattana-amorn S. The Development of Game Addiction Screening Test (GAST). *J Psychiatr Assoc Thailand*. 2014; 59(1): 3-14.
- [22] Bujang MA, Omar ED, Baharum NA. A Review on Sample Size Determination for Cronbach's Alpha Test: A Simple Guide for Researchers. *Malays J Med Sci*. 2018; 25(6): 85-99. doi: 10.21315/mjms2018.25.6.9
- [23] Hammell KW. Dimensions of meaning in the occupations of daily life. *Can J Occup Ther*. 2004; 71(5): 296-305. doi: 10.1177/000841740407100509
- [24] Khiaw-Im N, Aimyong N, Wongrathanandha C, Tangsangwornthamma C. Cross-Cultural Adaptation, Reliability, and Content Validity of Thai Version of Workplace Violence in the Health Sector Country Case Study Questionnaire. *J Prim Care Community Health*. 2022; 13: 1-5. doi: 10.1177/21501319221132448
- [25] Kim M, Yeom HE, Jung MS. Validation and psychometric properties of the multidimensional scale of perceived social support among Korean breast cancer survivors. *Asia Pac J Oncol Nurs*. 2022; 9(4): 229-35. doi: 10.1016/j.apjon.2022.01.004
- [26] Green SB, Yang Y, Alt M, Brinkley S, Gray S, Hogan T, et al. Use of internal consistency coefficients for estimating reliability of experimental task scores. *Psychon Bull Rev*. 2016; 23(3): 750-63. doi: 10.3758/s13423-015-0968-3
- [27] Townsend E, Wilcock AA. Occupational justice and client-centred practice: a dialogue in progress. *Can J Occup Ther*. 2004; 71(2): 75-87. doi: 10.1177/000841740407100203
- [28] Hinkamp D, Morton J, Krasnow DH, Wilmerding MV, Dawson WJ, Stewart MG, et al. Occupational Health and the Performing Arts: An Introduction. *J Occup Environ Med*. 2017; 59(9): 843-58. doi: 10.1097/JOM.0000000000001052
- [29] Gulu M, Yagin FH, Gocer I, Yapici H, Ayyildiz E, Clemente FM, et al. Exploring obesity, physical activity, and digital game addiction levels among adolescents: A study on machine learning-based prediction of digital game addiction. *Front Psychol*. 2023; 14: 1097145. doi: 10.3389/fpsyg.2023.1097145
- [30] Labana RV, Hadjisaid JL, Imperial AR, Jumawid KE, Lupague MJM, Malicdem DC. Online Game Addiction and the Level of Depression Among Adolescents in Manila, Philippines. *Cent Asian J Glob Health*. 2020; 9(1): e369. doi: 10.5195/cajgh.2020.369
- [31] Zaman M, Babar MS, Babar M, Sabir F, Ashraf F, Tahir MJ, et al. Prevalence of gaming addiction and its impact on sleep quality: A cross-sectional study from Pakistan. *Ann Med Surg (Lond)*. 2022; 78: 103641. doi: 10.1016/j.amsu.2022.103641
- [32] Yildiz Durak H, Haktanir A, Saritepeci M. Examining the Predictors of Video Game Addiction According to Expertise Levels of the Players: The Role of Time Spent on Video Gaming, Engagement, Positive Gaming Perception, Social Support and Relational Health Indices. *Int J Ment Health Addict*. 2023; 9: 1-26. doi: 10.1007/s11469-023-01073-3

- [33] Guskowska M, Dabrowska-Zimakowska A. Occupational balance, changes in occupations and psychological well-being of university students during the COVID-19 pandemic. *Scand J Occup Ther.* 2023; 30(4): 463-74. doi: 10.1080/11038128.2022.2143892
- [34] WHO Guideline on Self-Care Interventions for Health and Well-Being. WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2021.

Psychometric properties of the self-report questionnaire on occupational balance in university students with game addiction

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ABSTRACT

Background: The prevalence of adolescents and young adults playing games on the internet is increasing worldwide. However, excessive game playing can cause game addiction among adolescents. Studies have demonstrated that game addiction increases the risks of physical and mental health problems, leading to occupational performance issues. Nevertheless, what level of game addiction impacts health issues is controversial. Therefore, this study focused on occupational balance, an individual's perception of a proper amount and diversity of activities. The study demonstrated that occupational imbalance could lead to a decrease in an individual's occupational performance. However, an appropriate instrument for screening occupational balance in young adults with game addiction has never been studied yet, especially in a Thai version.

Objective: This study aimed to develop a self-report questionnaire on occupational balance for Thai university students with game addiction.

Materials and methods: The questionnaire consisted of 21 items divided into four dimensions, including the individual's perceptions of participating in meaningful activities, having the proper proportion of time to perform occupations, having the appropriate variety of occupations, and being satisfied with their health and well-being. In addition, the psychometric properties of a questionnaire were investigated.

Results: The questionnaire had sufficient validity and good internal consistency for screening occupational balance in Thai university students with game addiction. The questionnaire was divided into four dimensions, each with good construct validity and internal consistency.

Conclusion: The questionnaire was valid and reliable for evaluating occupational balance for Thai university students with game addiction. This information can provide a new occupational therapy instrument for identifying occupational balance in the population with game addiction.

Introduction

Nowadays, the prevalence of adolescents and young adults playing games on the internet is increasing worldwide.¹ Subsequently, the studies indicated that excessive game playing can result in numerous physical and mental health problems,² including game addiction.³ This is consistent with evidence of game addiction increasing progressively in the adolescent and young adult population.⁴ In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the World Health Organization (WHO) reported that internet gaming disorder or game addiction is a mental health condition defined as a continuous and repetitive pattern of gaming behavior.³

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Studies have shown that game addiction can lead to various public health issues, including impaired emotional control, attention deficit, and cognitive dysfunction.^{5,6} They also concurred that game addiction among adolescents increases the risks of physical and mental health problems, thus leading to occupational performance issues such as poor sleep quality.⁷ This aligns with studies reporting that game addiction decreases the chance of interpersonal interactions and good school performance.^{8,9} However, the severity of game addiction's impact on occupational performance remains controversial. Some studies have suggested that game playing can be beneficial in various ways, such as increased relaxation, cognitive processing, and visual perception.^{10,11} Therefore, researchers are looking for suitable predictors to screen occupational performance issues in individuals with game addiction.

It is known that occupational balance is one of the critical concepts used in occupational therapy interventions. Studies have shown that occupational balance relates to an individual's occupational performance.^{12,13} It is consistent with a study that demonstrated that occupational imbalance increases the risk of stress-related disorders and leads to an individual's poor occupational performance.¹⁴ Therefore, this study focuses on the concept of occupational balance for screening occupational balance issues in Thai university students with game addiction. Currently, many occupational therapists define occupational balance as an individual's satisfaction with their health and well-being.¹⁵ Some studies suggested that occupational balance involves an equilibrium of self-care, leisure, play, work, education, and sleep.¹⁶ In contrast, others define it as an individual's perception of having a proper amount and variety of activities.¹⁷ This study proposed a new definition of occupational balance,^{15,17-19} which includes four dimensions: 1) participation in meaningful activities, 2) appropriate allocation of time to perform occupations, 3) having an appropriate variety of occupations, and 4) satisfaction with health and well-being.

Occupational therapists are developing instruments or questionnaires to assess an individual's occupational balance. For example, Dur *et al.*¹⁹ developed a self-reported occupational balance questionnaire focusing on patients' perspectives rather than those of occupational therapists.¹⁹ Moreover, Wagman and Håkansson developed the Occupational Balance Questionnaire (OBQ), emphasizing satisfaction with the number and variety of occupations.²⁰ However, an appropriate instrument for screening occupational balance in young adults with game addiction has not been studied, especially in a Thai context.

Thus, this study developed a self-report questionnaire on occupational balance for Thai university students with game addiction based on the new definition mentioned above. The psychometric properties in designing the questionnaire were also investigated in this population. It is hoped that this research will provide a new occupational therapy instrument to identify occupational balance in adolescents and young adults with game addiction.

Materials and methods

Participants

The participants in this study were undergraduate students from Chiang Mai University. The inclusion criteria were: (1) being an undergraduate student, (2) having no history of psychiatric disorders, and (3) having no physical disabilities. Ethics approval was granted by the ethics committee of the faculty of Associated Medical Sciences, Chiang Mai University (Ethic number: AMSEC-66EX-034). All participants provided written informed consent.

The sample size calculation was calculated using G*Power software 3.1.9.7 (effect size=0.4, power of test=0.8, alpha=0.05, a two-tailed test). In this study, 200 undergraduate students were divided into two groups of 100 individuals: one group with game addiction and the other without it, to test construct validity using the known group technique. Game addiction was assessed using the game addiction screening test for children and adolescents.²¹ Additionally, the sample size for measuring the reliability of internal consistency was calculated using Bonett's formula.²² A single coefficient of Cronbach's alpha test was used to calculate the sample size. According to Bonett's formula, the value of Cronbach's alpha at null hypothesis (CA0) and the expected value of Cronbach's alpha (CA1) could be any value ranging from -1 to 1. CA0 is more than zero if the researcher assumes a high internal consistency of the questionnaire items.²² Thus, this study set the values of CA0 and CA1 as 0.55 and 0.7, respectively. It is known that the good power of a test can be 0.8 or greater. Therefore, the power of the test was set at 0.8 in this study. Moreover, the number of items in the questionnaire (k) and the probability of type I error (alpha) were also set as 21 and 0.05, respectively. Finally, one hundred and three undergraduate students with game addiction were used to measure internal consistency reliability (CA0=0.55, CA1=0.7, alpha=0.05, and power of test=0.8, k=21).

Research design of this study

Phase 1: Development of the self-report questionnaire on occupational balance for university students with game addiction.

The self-report questionnaire, featuring five Likert rating scales, was developed based on the occupational science tenet. According to occupational science, engaging in meaningful activities enhances individuals' awareness of their abilities and self-worth.²³ However, such engagement in meaningful activities should be balanced across various aspects, including participation in diverse daily activities, appropriate allocation of time to perform each activity, and overall satisfaction with health and well-being.^{17,18} In addition, occupational balance considers the perspective of roles, which are unique and vary for each person.¹⁹ Therefore, the developed questionnaire in this study consisted of five Likert rating scales with items of question to evaluate individuals' perceptions in four dimensions. The five Likert rating scales measured levels of agreement for each item: 1 point = strongly disagree, 2 points = disagree, 3 points = neither agree nor disagree, 4 points =

agree, and 5 points = strongly agree.

Subsequently, the content validity of the questionnaire was evaluated by five experts: 1) a psychiatrist who has experienced working with children and adolescents with game addiction; 2) an occupational therapist specializing in occupational balance; 3) two occupational therapists experienced in treating individuals with mental health problems; and 4) an occupational therapist experienced in developing occupational therapy assessment tools. In this study, a psychiatrist is a validator of questionnaires looking into the behavior of game addiction, such as the amount of time and frequency of game playing. Occupational therapists experienced in treating individuals with mental health problems are the validators of questionnaires looking into the game addict's perception of participating in

meaningful activities as well as the impact of game addiction on occupations. An occupational therapist specializing in occupational balance validates questionnaires looking into the accuracy of all relevant aspects of occupational balance. Moreover, an occupational therapist experienced in developing occupational therapy assessment tools is a validator of questionnaires looking into the precision of occupational therapy assessment tools. After that, the developed questionnaire was adjusted following experts' recommendations and was tested in a pilot study with 12 college students with gaming addiction. Finally, the self-report questionnaire consisted of five Likert rating scales with 21 items to evaluate individuals' perceptions in the four dimensions above. Each item of the questionnaire is shown in Table 1.

Table 1. Items of the self-report questionnaire on occupational balance in university students with game addiction.

Items of the questionnaire	Questions
Dimension 1: Individual's perception of participating in meaningful activities	
1	Basic activities of daily living hold meaning and value for you.
2	Instrumental activities of daily living hold meaning and value for you.
3	Health management activities hold meaning and value for you.
4	Rest and sleep activity hold meaning and value for you.
5	Education holds meaning and value for you.
6	Work holds meaning and value for you.
7	Leisure activities hold meaning and value for you.
8	Social participation activities hold meaning and value for you.
Dimension 2: Individual's perception of having the proper amount of time to engage occupations	
9	Each day, you allocate an appropriate time for each activity.
10	The distribution of time among occupations each day is appropriate.
11	Despite playing game every day or almost every day, you can still effectively manage your time and daily activities.
Dimension 3: Individual's perception of having a suitable range of occupations	
12	Each day, you typically engage in a variety of activities.
13	Your daily activities contribute to a good quality of life.
14	You prefer to focus on activities that align with your role each day.
15	Engaging in a variety of activities brings you happiness.
16	Each week, you often make time for activities outside of your education or work commitments.
Dimension 4: Individual's perception of being satisfied with their health and well-being	
17	You are content with your physical health.
18	You are content with your mental health.
19	You are satisfied with your relationships with close individuals such as family, close friends, and partners.
20	You are satisfied with your relationships with others, such as colleagues and strangers.
21	You are satisfied with your physical environment where you engage in activities.

Phase 2: Study of psychometric properties of the questionnaire.

In this study, the questionnaire's psychometric properties, including content validity, construct validity, and reliability, were investigated. Five experts assessed Content validity using the index of item-objective congruence (IOC), while construct validity was examined using the known-group technique. Additionally, internal consistency reliability was investigated in young adults with game addiction.

Data analysis

An IOC value of 0.5 or higher was considered acceptable.²⁴ Construct validity was tested using the known-group technique and analyzed with an independent t-test.²⁵ If the average scores of the two groups (those with and without game addiction) were significantly different, the questionnaire was regarded to have good construct validity.²⁵ Internal consistency of the questionnaire was assessed using Cronbach's alpha.²⁶ A Cronbach's alpha value of 0.7 or higher indicated good internal consistency.²⁶

A two-sided p-value of 0.05 was considered significant for all statistical tests.

Results**Demographic data of the participants**

The demographic data of the participants are shown in Table 2. The results showed that the average age of the participants in the groups with and without game addiction was 19.70 ± 1.29 and 20.02 ± 1.21 , respectively. Regarding financial status, the average monthly income in the groups with and without game addiction was 8387.37 ± 5862.28 and 7730.39 ± 4926.78 Baht, respectively. Furthermore, the average monthly expense related to games in groups with and without game addiction was 532.81 ± 781.22 and 49.23 ± 115.26 Baht, respectively. For time spent playing games, the average game time per day and week in the group with game addiction was 106.12 ± 63.15 min and 5.44 ± 1.62 days, respectively, while the average game time per day and week in the group without game addiction was 80.21 ± 66.92 minutes and 3.53 ± 2.42 days, respectively.

Table 2. Demographic data of participants.

Variables	Group with game addiction (N=103)	Group without game addiction (N=103)
Gender		
Male (N, %)	34, 33.01%	42, 40.78%
Female (N, %)	69, 66.99%	61, 59.22%
Age average (years)	19.70 ± 1.29	20.02 ± 1.21
Academic year		
1 st year (N, %)	34, 33.01%	39, 37.86%
2 nd year (N, %)	20, 19.42%	30, 29.13 %
3 rd year (N, %)	46, 44.66%	20, 19.42%
4 th year (N, %)	1, 0.97%	13, 12.62%
>4 th year (N, %)	2, 1.94%	1, 0.97%
Financial status		
Average income/month (Baht)	8387.37 ± 5862.28	7730.39 ± 4926.78
Average expense related to game/ month (Baht)	532.81 ± 781.22	49.23 ± 115.26
Time spent game playing		
Average game time per day (min)	106.12 ± 63.15	80.21 ± 66.92
Average game time per week (days)	5.44 ± 1.62	3.53 ± 2.42

Content validity of the self-report questionnaire on occupational balance for young adults with game addiction

The content validity of the questionnaire was tested using the index of item objective congruence (IOC) by five experts. Based on their recommendations, the questionnaire was revised to include definitions and examples of technical terms for better clarity for respondents. Finally, the 21-item questionnaire was used to test content validity. The results showed high overall congruences (IOC=0.92), particularly on the following dimensions: 1) participation in meaningful activities (IOC=0.93), 2) proper allocation of time to perform occupations (IOC=0.95), 3) appropriate variety of occupations (IOC=0.88), and 4) satisfaction with health and well-being (IOC=0.96).

Construct validity of the self-report questionnaire on occupational balance for young adults with game addiction

The construct validity of the self-report questionnaire was assessed to determine its effectiveness in evaluating occupational balance (Table 3). This assessment was conducted using the known-group technique with an independent t-test analysis. This result suggested that the questionnaire had good construct validity. Furthermore, the questionnaire revealed significant differences between the groups in each dimension: dimension 1 ($p=0.001$); dimension 2 ($p=0.002$); dimension 3 ($p=0.001$); and dimension 4 ($p=0.003$) (Table 3).

Table 3. Construct validity of questionnaire.

Items of questionnaire	Group with game addiction (N=100) (Mean±SD)	Group without game addiction (N=100) (Mean±SD)	p value
Average score of total items of the questionnaire	78.59±9.02	86.26±8.91	0.000*
Average score of all items in dimension 1	34.33±3.69	35.87±3.03	0.001*
Average score of all items in dimension 2	9.38±3.60	11.33±2.76	0.000*
Average score of all items in dimension 3	16.48±5.92	19.24±3.27	0.000*
Average score of all items in dimension 4	18.40±3.71	19.82±3.01	0.003*

Note: * $p < 0.05$ indicates the statistically significant average questionnaire scores between groups with and without game addiction.

Dimensions 1 to 4 correspond to the individual's perceptions of participating in meaningful activities, having the proper amount of time to engage in occupations, having a suitable range of occupations, and being satisfied with their health and well-being, respectively.

Reliability of the self-report questionnaire on occupational balance for young adults with game addiction

The sample used to investigate the internal consistency reliability was the same as the known-group technique cohort, explicitly focusing on individuals with game addiction. The test results using Cronbach's alpha coefficient indicated that all questionnaire items had a Cronbach's alpha coefficient of 0.83. Moreover, each dimension of the questionnaire demonstrated the following: dimension 1 (Cronbach's alpha=0.66), dimension 2 (Cronbach's alpha=0.71), dimension 3 (Cronbach's alpha=0.76), and dimension 4 (Cronbach's alpha=0.80).

Discussion

Some studies have shown that game playing has beneficial effects, such as enhancing cognitive function and promoting relaxation.^{10,11} However, excessive game playing can cause several public health problems, such as impaired emotional control, attention deficits, or cognitive dysfunction, leading to game addiction.^{5,6} Therefore, deciding what level of game addiction impacts health issues is controversial. This study focused on occupational balance, defined as the equilibrium in performing daily occupations, such as self-care, education, work, leisure, and play.¹⁶ It is possible that excessive time spent on one activity, such as game playing, may cause loss of occupational balance and lead to health issues. This is consistent with the definition of occupational imbalance, which is spending excessive time on one activity, leading to poor quality of life.¹⁸⁻²⁷ Additionally, studies have reported that occupational balance is related to individual occupational performance.^{12,13} It is known that occupational performance is an essential component for exploring health issues.²⁸ Therefore, it seems likely that occupational imbalance caused by game addiction may lead to a deficit in occupational performance in game addicts and lead to poor quality of life. This is consistent with studies that demonstrate the effects of game addiction on performance and effectiveness in daily life activities such as sleep, education, and work achievement. Game addiction also affects participation in daily life activities of individuals through a loss of emotional control, attention deficit, and cognitive impairment.^{8,9,29-31} Therefore, the concept of occupational balance may be

used as a predictor of health issues in game addicts via decreasing occupational performance in daily occupations and activities relevant to the role of the individual.

Occupational therapists are currently developing instruments or questionnaires to assess the occupational balance of an individual based on its definition. Many occupational therapists clarify the meaning of occupational balance differently, such as perspectives of an individual on participation in diverse daily activities, appropriate allocation of time spent in performing each activity, or satisfaction with health and well-being.^{17,18} However, there are no instruments or questionnaires for evaluating all definitions of occupational balance. For example, a self-reported occupational balance questionnaire focuses on the patient's perspectives rather than those of occupational therapists.¹⁹ In contrast, the Occupational Balance Questionnaire (OBQ) focuses on satisfaction.²⁰ Therefore, the questionnaire in this study was developed based on a new definition that focuses not only on the appropriate amount of variety and time spent on daily activities but also on the importance of satisfaction with health and well-being and doing purposeful and meaningful activities. This study developed a Thai version of the instrument to screen occupational balance in individuals with game addiction, based on the new concept of occupational balance in four dimensions: participation in meaningful activities, appropriate allocation of time to perform occupations, having an appropriate variety of occupations, and satisfaction with health and well-being. After that, the psychometric properties testing of the questionnaire was conducted. It was found that this study is the first to validate and establish reliability of such a questionnaire for Thai university students with game addiction. Moreover, the psychometric properties in each dimension of the questionnaire were tested, and the results were as follows.

In dimension 1, eight questionnaire items assess an individual's participation in meaningful activities. It has been known that occupational balance consists of both the temporal aspect and of the valued or meaningful occupations.¹⁸ The results of this study showed that dimension 1 of the questionnaire has good content and construct validity. This finding indicates that the questionnaire can accurately measure an individual's perception of participating in meaningful activities.

However, the internal consistency of items in dimension 1 was questionable (Cronbach's $\alpha=0.66$), indicating response variability. This variability may stem from differences in how individuals perceive participation in meaningful activity. Additionally, individuals may have distinct characteristics and daily occupational patterns that influence their lifestyle. For example, some individuals may find education significant, while others may not. Thus, the internal consistency value of items in dimension 1 reflected variation in responses.

In dimension 2, three questionnaire items assess the individual's perception of having a proper proportion of time to perform activities. It is consistent with a study that defined occupational balance as an individual's perception of adequate time spent on each activity.¹⁸ Another study demonstrated that game addiction is positively correlated with increased time spent playing games,³² which can subsequently lead to an inability to perform daily activities and result in occupational imbalance. The results of this study showed that the items in dimension 2 have acceptable levels of validity and reliability. Therefore, the questionnaire is suggested to be an effective tool for measuring occupational balance among Thais addicted to game playing, specifically in the dimension of having a proper proportion of time to perform occupations.

In dimension 3, five questionnaire items assess the individual's perception of having the appropriate variety of occupations. It is consistent with a study that reported that a variety of occupations is an important aspect of occupational balance.¹⁷ Furthermore, occupational balance emphasizes doing or engaging in a diverse range of occupations,¹⁷ related to health and well-being.³³ This study found that the validity and reliability of items in dimension 3 were acceptable. Therefore, the questionnaires are recommended as an effective tool for measuring occupational balance among Thais addicted to game playing, specifically regarding having the appropriate variety of occupations.

In dimension 4, five questionnaire items assess the individual's perception of satisfaction with health and well-being. It is established that health and well-being are closely related to occupational balance.¹⁸ The items in dimension 4 represent physical, mental, and social engagement satisfaction, aligning with the World Health Organization's definition of health and well-being.³⁴ This study's results indicated that the validity and reliability of items in dimension 4 were acceptable. Therefore, the questionnaire has the potential to effectively measure the satisfaction of Thais addicted to game playing with their health and well-being.

This study developed a new instrument for evaluating occupational balance, focusing on an individual's perception of performing daily activities in four dimensions, as mentioned above. Occupational balance is unique to each person and reflects their specific occupations and lifestyle performances. The value and meaning of occupations may vary among individuals. This study demonstrated that the questionnaire has acceptable validity and reliability for assessing occupational balance among Thai adolescents

and young adults with game addiction. However, this study cannot test the exploratory factor analysis due to the limited sample size. In the future, the questionnaire needs to be tested to confirm the construct validity. Therefore, it suggested that the findings of this study can contribute to the development of new occupational therapy tools for identifying and addressing occupational balance issues in populations addicted to gaming. Moreover, it can serve as a valuable tool for exploring individual occupational concerns and for future planning of occupational therapy interventions for Thais addicted to game playing.

Conclusions

This pioneering study demonstrated that the self-report questionnaire exhibits acceptable validity and reliability in evaluating occupational balance among Thai adolescents and young adults with game addiction. These findings introduce a new occupational therapy instrument to identify occupational balance issues in such a population.

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Conflict of interest

The authors declare no conflict of interest.

References

- [1] Kim D, Lee J. Addictive Internet Gaming Usage among Korean Adolescents before and after the Outbreak of the COVID-19 Pandemic: A Comparison of the Latent Profiles in 2018 and 2020. *Int J Environ Res Public Health*. 2021; 18(14). doi: 10.3390/ijerph18147275
- [2] Basdas O, Ozbey H. Digital game addiction, obesity, and social anxiety among adolescents. *Arch Psychiatr Nurs*. 2020; 34(2): 17-20. doi: 10.1016/j.apnu.2019.12.010
- [3] Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry*. 2013; 12(2): 92-8. doi: 10.1002/wps.20050
- [4] Gao YX, Wang JY, Dong GH. The prevalence and possible risk factors of internet gaming disorder among adolescents and young adults: Systematic reviews and meta-analyses. *J Psychiatr Res*. 2022; 154: 35-43. doi: 10.1016/j.jpsychires.2022.06.049
- [5] Zhao W, Wei T, Zhou R, Wang Y, Wang Y, Ren Z, et al. The Influence of Online Game Behaviors on the Emotional State and Executive Function of College Students in China. *Front Psychiatry*. 2021; 12: 713364. doi: 10.3389/fpsyt.2021.713364
- [6] Dong G, Li H, Wang L, Potenza MN. Cognitive control and reward/loss processing in Internet gaming disorder: Results from a comparison with recreational Internet game-users. *Eur Psychiatry*. 2017; 44: 30-8. doi: 10.1016/j.eurpsy.2017.03.004
- [7] Alghamdi FAD, Alghamdi FAG, Abusulaiman A,

- Alsulami AJ, Bamotref M, Alosaimi A, et al. Video Game Addiction and its Relationship with Sleep Quality among Medical Students. *J Epidemiol Glob Health*. 2024; 19: 1-8. doi: 10.1007/s44197-024-00265-x
- [8] Yang SY, Wang YC, Lee YC, Lin YL, Hsieh PL, Lin PH. Does Smartphone Addiction, Social Media Addiction, and/or Internet Game Addiction Affect Adolescents' Interpersonal Interactions? *Healthcare*. 2022; 23;10: 963-77. doi: 10.3390/healthcare10050963
- [9] Van den Eijnden R, Koning I, Doornwaard S, van Gurp F, Ter Bogt T. The impact of heavy and disordered use of games and social media on adolescents' psychological, social, and school functioning. *J Behav Addict*. 2018; 7(3): 697-706. doi: 10.1556/2006.7.2018.65
- [10] Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. Brains on video games. *Nat Rev Neurosci*. 2011; 12(12): 763-8. doi: 10.1038/nrn3135
- [11] Feng J, Spence I, Pratt J. Playing an action video game reduces gender differences in spatial cognition. *Psychol Sci*. 2007; 18(10): 850-5. doi: 10.1111/j.1467-9280.2007.01990.x
- [12] Martin Perez AM, Maximo-Bocanegra N, Rivas Ruiz F, Alguacil-Diego IM, Martinez-Piedrola RM. [Occupational balance, disability and functionality in people with rheumatic disease]. *An Sist Sanit Navar*. 2023; 46(3): e1053-62. doi: 10.23938/ASSN.1053
- [13] Magnusson L, Hakansson C, Brandt S, Oberg M, Orban K. Occupational balance and sleep among women. *Scand J Occup Ther*. 2021; 28(8): 643-51. doi: 10.1080/11038128.2020.1721558
- [14] Hakansson C, Ahlborg G, Jr. Occupational imbalance and the role of perceived stress in predicting stress-related disorders. *Scand J Occup Ther*. 2018; 25(4): 278-87. doi: 10.1080/11038128.2017.1298666
- [15] AA. W. An occupational perspective of health. 2nd ed. ed: Thorofare, NJ: Slack.; 2006.
- [16] Nurit W, Michal AB. Rest: a qualitative exploration of the phenomenon. *Occup Ther Int*. 2003; 10(4): 227-38. doi: 10.1002/oti.187
- [17] Wagman P, Hakansson C, Bjorklund A. Occupational balance as used in occupational therapy: a concept analysis. *Scand J Occup Ther*. 2012; 19(4): 322-7. doi: 10.3109/11038128.2011.596219
- [18] Backman CL. Occupational balance: exploring the relationships among daily occupations and their influence on well-being. *Can J Occup Ther*. 2004; 71(4): 202-9. doi: 10.1177/000841740407100404
- [19] Dur M, Steiner G, Fialka-Moser V, Kautzky-Willer A, Dejaco C, Prodinger B, et al. Development of a new occupational balance-questionnaire: incorporating the perspectives of patients and healthy people in the design of a self-reported occupational balance outcome instrument. *Health Qual Life Outcomes*. 2014; 12: 45. doi: 10.1186/1477-7525-12-45
- [20] Wagman P, Hakansson C. Introducing the Occupational Balance Questionnaire (OBQ). *Scand J Occup Ther*. 2014; 21(3): 227-31. doi: 10.3109/11038128.2014.900571
- [21] Pornnoppadol P. SB, Khamklieng K., Pattana-amorn S. The Development of Game Addiction Screening Test (GAST). *J Psychiatr Assoc Thailand*. 2014; 59(1): 3-14.
- [22] Bujang MA, Omar ED, Baharum NA. A Review on Sample Size Determination for Cronbach's Alpha Test: A Simple Guide for Researchers. *Malays J Med Sci*. 2018; 25(6): 85-99. doi: 10.21315/mjms2018.25.6.9
- [23] Hammell KW. Dimensions of meaning in the occupations of daily life. *Can J Occup Ther*. 2004; 71(5): 296-305. doi: 10.1177/000841740407100509
- [24] Khiaw-Im N, Aimyong N, Wongrathanandha C, Tangsangwornthamma C. Cross-Cultural Adaptation, Reliability, and Content Validity of Thai Version of Workplace Violence in the Health Sector Country Case Study Questionnaire. *J Prim Care Community Health*. 2022; 13: 1-5. doi: 10.1177/21501319221132448
- [25] Kim M, Yeom HE, Jung MS. Validation and psychometric properties of the multidimensional scale of perceived social support among Korean breast cancer survivors. *Asia Pac J Oncol Nurs*. 2022; 9(4): 229-35. doi: 10.1016/j.apjon.2022.01.004
- [26] Green SB, Yang Y, Alt M, Brinkley S, Gray S, Hogan T, et al. Use of internal consistency coefficients for estimating reliability of experimental task scores. *Psychon Bull Rev*. 2016; 23(3): 750-63. doi: 10.3758/s13423-015-0968-3
- [27] Townsend E, Wilcock AA. Occupational justice and client-centred practice: a dialogue in progress. *Can J Occup Ther*. 2004; 71(2): 75-87. doi: 10.1177/000841740407100203
- [28] Hinkamp D, Morton J, Krasnow DH, Wilmerding MV, Dawson WJ, Stewart MG, et al. Occupational Health and the Performing Arts: An Introduction. *J Occup Environ Med*. 2017; 59(9): 843-58. doi: 10.1097/JOM.0000000000001052
- [29] Gulu M, Yagin FH, Gocer I, Yapici H, Ayyildiz E, Clemente FM, et al. Exploring obesity, physical activity, and digital game addiction levels among adolescents: A study on machine learning-based prediction of digital game addiction. *Front Psychol*. 2023; 14: 1097145. doi: 10.3389/fpsyg.2023.1097145
- [30] Labana RV, Hadjisaid JL, Imperial AR, Jumawid KE, Lupague MJM, Malicdem DC. Online Game Addiction and the Level of Depression Among Adolescents in Manila, Philippines. *Cent Asian J Glob Health*. 2020; 9(1): e369. doi: 10.5195/cajgh.2020.369
- [31] Zaman M, Babar MS, Babar M, Sabir F, Ashraf F, Tahir MJ, et al. Prevalence of gaming addiction and its impact on sleep quality: A cross-sectional study from Pakistan. *Ann Med Surg (Lond)*. 2022; 78: 103641. doi: 10.1016/j.amsu.2022.103641
- [32] Yildiz Durak H, Haktanir A, Saritepeci M. Examining the Predictors of Video Game Addiction According to Expertise Levels of the Players: The Role of Time Spent on Video Gaming, Engagement, Positive Gaming Perception, Social Support and Relational Health Indices. *Int J Ment Health Addict*. 2023; 9: 1-26. doi: 10.1007/s11469-023-01073-3
- [33] Guskowska M, Dabrowska-Zimakowska A. Occupational

balance, changes in occupations and psychological well-being of university students during the COVID-19 pandemic. *Scand J Occup Ther.* 2023; 30(4): 463-74. doi: 10.1080/11038128.2022.2143892

[34] WHO Guideline on Self-Care Interventions for Health and Well-Being. WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2021.

Analyzing *dprE1* gene variations in drug-resistant *Mycobacterium tuberculosis* isolates from Northern Thailand

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ABSTRACT

Background: DprE1 has been discovered as a highly promising candidate for eradicating multidrug-resistant tuberculosis (MDR-TB) due to its localization and crucial role in cell wall synthesis. Several DprE1 inhibitors in clinical trials target different binding sites on the DprE1 protein. However, mutations in these binding sites can result in resistance to these inhibitors. Nonetheless, only a few reports exist on the sequence analysis of the *dprE1* gene in drug-resistant clinical isolates, especially in Thailand, a country with a high TB burden.

Objective: To investigate the genetic variations in the *dprE1* gene among drug-resistant clinical *Mycobacterium tuberculosis* (Mtb) isolates from Northern Thailand and to examine mutations known to confer resistance to specific inhibitors.

Materials and methods: Drug resistance profiles of 19 clinical Mtb isolates from Northern Thailand—11 multidrug-resistant Mtb, 2 isoniazid-resistant Mtb, and 6 rifampicin-resistant Mtb—were assessed using the agar proportion method and Sanger sequencing. New PCR and sequencing primers were designed to cover the entire length of the *dprE1* gene. Mutation profiles were detected by performing DNA alignment against the reference strain, *M. tuberculosis* H37Rv, using BioEdit Sequence Alignment version 7.2.5. The distribution of these mutations was assessed through the Basic Local Alignment Search Tool (BLAST) server. Visual representation of amino acid mutation regions in DprE1 was generated using the PyMOL 3.0.

Results: The mutation at codon 387 associated with benzothiazinone (BTZ) compounds was not observed in the *dprE1* gene of any clinical isolates. The most common mutation profile, C→T at codon 459, was found in 73.68% of clinical isolates. However, this is a silent mutation and probably indicates genetic polymorphism. Non-synonymous substitutions in the *dprE1* gene were detected: A356T in one INH-R isolate and V400I in two RIF-R isolates. BLAST analysis revealed that the A356T mutation in the INH-R isolates had a 100% match with sixteen Mtb strains from other regions. Interestingly, the V400I mutation in the RIF-R isolates had not been reported, making this the first documentation of such a finding.

Conclusion: Although no mutations directly linked to resistance against current DprE1 inhibitors were found, mutations in the DprE1 binding sites could affect the efficacy of these inhibitors. This study highlights the significance of mono-drug-resistant strains that acquire *dprE1* mutations, potentially complicating future TB treatment targeting DprE1.

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Introduction

Tuberculosis (TB) remains one of the global burden diseases, with approximately 1.5 million deaths and more than 10 million new cases yearly.¹ The occurrence of new cases is associated with the reactivation of latent TB infection, possibly due to poverty, malnutrition, and its

coexistence with HIV/AIDS.² Despite the significant efficacy of existing anti-TB drugs, the non-compliance by patients and the complex defense mechanisms of *Mycobacterium tuberculosis* (Mtb) can lead to the development of drug resistance.^{3,4} Currently, eradication of multidrug-resistant TB (MDR-TB), which is expressed as resistance to two first-line antibiotics, isoniazid (INH) and rifampicin (RIF), is the main challenge in TB control.⁵ Failure to effectively treat MDR-TB can lead to the emergence of extensively drug-resistant TB (XDR-TB), highlighting the need to explore new molecular targets for treatment.

The mycobacterial cell wall is unique due to its lipid-rich, complex structure, which protects Mtb from the harsh environment of the host and its antibiotic effects.⁶ Consequently, cell wall synthesis plays an essential process in Mtb survival, and genes involved in this

pathway become the target of the first-line drugs such as isoniazid and ethambutol, which inhibit mycolic acid and arabinogalactan synthesis of the cell wall of Mtb, respectively.⁷ The flavoenzyme Decaprenylphosphoryl- β -D-ribose-2'-epimerase oxidase (DprE1, Rv-3790) is an essential enzyme involved in the synthesis of the arabinan components of lipoarabinomannan (LAM) and arabinogalactan (AG), both of which are important for cell wall integrity and immunomodulatory role of Mtb.^{8,9} DprE2 and DprE1 facilitate the two-step epimerization of decaprenyl-phospho-ribose (DPR). Initially, DprE1 catalyzes the conversion of DPR into decaprenyl-phospho-20-keto-D-arabinose (DPX), with a concurrent reduction of the FAD cofactor to FADH₂. Subsequently, DPX is reduced to DPA by DprE2, serving as the exclusive precursor for the synthesis of AG and LAM (Figure 1).¹⁰

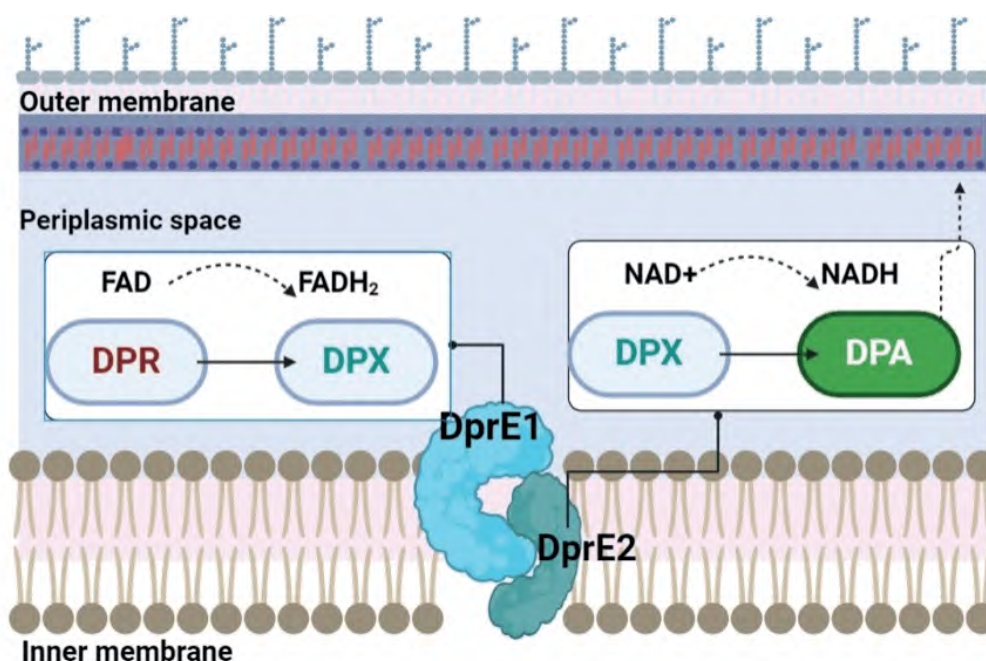


Figure 1. The role of DprE1 and DprE2 in cell wall components construction. Created with Biorender (biorender.com).

DprE1 is often described as a “magic drug target” because it is highly conserved in Mtb and the epimerization process it mediates occurs in the periplasmic space, which makes it more accessible to inhibitors.^{8,11} DprE1 was initially identified as a target of benzothiazinones (BTZ), which irreversibly inhibit the enzyme by forming a covalent adduct with the amino acid Cysteine at codon 387 (Cys387).¹² In contrast, some noncovalent inhibitors, such as TBA-7371, act as competitive inhibitors.¹⁰ Both covalent and non-covalent inhibitors targeting DprE1, including Macozinone, BTZ-043, and TBA-7371, are currently undergoing clinical trials.¹³ However, it remains crucial to identify any mutations in clinical isolates of Mtb because, unlike Mtb, *M. avium* and *M. aurum* have serine or alanine at position 387, which leads to natural resistance to BTZ.^{12,14}

Researchers monitored potential BTZ resistance in a study by analyzing the DprE1 sequences of Mtb clinical isolates from four European Hospitals. They found all

isolates were susceptible to BTZ and lacked mutations in the Cys387 region. This study concluded that mutations associated with BTZ resistance are not present in the currently circulating strains of Mtb.¹⁵ However, as most strains in this study were from drug-susceptible (DS) TB cases, further research is needed to analyze the genetic variation of the DprE1 in MDR-TB clinical isolates. This is essential because drugs targeting DprE1 are critical for treating MDR-TB, and comprehensive information on mutations in DprE1 from drug-resistant clinical isolates in Northern Thailand remains limited.

Therefore, the present study aims to investigate the genetic diversity and identify mutations of the *dprE1* gene in MDR-TB and mono-resistance to isoniazid and rifampicin isolates from Northern Thailand. The findings would reveal patterns of mutation in the *dprE1* gene. This may contribute to developing new drugs that avoid common mutation sites for interaction, thereby improving the treatment of drug-resistant TB.

Materials and methods

Mycobacterial strains

The Mtb strains exhibiting diverse drug resistance profiles (11 MDR, 2 INH-R, and 6 RIF-R) were kindly provided by the Office of Disease Prevention and Control 1 (Chiang Mai, Thailand). These strains were isolated from TB patients in Northern Thailand between 2015 and 2019. Lowenstein-Jensen (L-J) medium (Biomedica, Thailand) was used to culture all Mtb clinical isolates at 37 °C for 1 month.

Determination of drug-resistant profiles

The agar proportion method was used to perform standard drug susceptibility testing (DST) of Mtb isolates against first-line anti-TB drugs. As previously described, an isolate was classified as resistant if more than 1% of the colony grew on Middlebrook 7H10 agar plates when exposed to the critical drug concentrations: 0.2 µg/mL for isoniazid (INH), 1.0 µg/mL for rifampicin (RIF), 2.0 µg/mL for streptomycin (SM), and 5.0 µg/mL for ethambutol (EMB).¹⁶ Additionally, the mutation profiles of each isolate were confirmed by DNA sequencing. This included identifying *rpoB* mutations associated with rifampicin resistance (RIF-R) and mutations in *katG* and *inhA* genes linked to isoniazid resistance (INH-R).

Design of sequencing primers

Using the Primer-BLAST program (NCBI), primers were designed to cover the entire length of the *dprE1* gene (1385 bp) based on the nucleotide sequence (4235779-4237164) of *dprE1* gene in *M. tuberculosis* H37Rv, complete genome (CP003248.2). The forward primer, *dprE1_F*, is 5'-GTCGGACTCAACCACCTCTG-3' and reverse primer, *dprE1_R*, is 5'-GATCAAAAAGCCGAAGCGCC-3'.

DNA extraction and PCR amplification of the *dprE1* gene

The genomic DNA of each Mtb clinical isolate was extracted according to the manufacturer's instructions

using the Anyplex™ II MTB/MDR Detection kit (see gene, the Republic of South Korea). The extracted DNA was kept at -20 °C before use. PCR amplification of the *dprE1* gene was performed using the newly designed primers. The 50-µL PCR reaction included KOD One™ PCR Master Mix (Toyobo, Japan), 0.3 µM of primers, and 100 ng of DNA template. The PCR conditions were carried out as follows: initial denaturation at 94 °C for 2 min, followed by 30 cycles consisting of denaturation at 95 °C for 30 sec, annealing at 68 °C for 15 sec, and extension at 72 °C for 10 sec, followed by 72 °C for 2 min as a final extension. The resulting DNA fragments were examined by electrophoresis on a 1.5% (w/v) agarose gel at 80 volts and visualized using ethidium bromide staining. Before Sanger sequencing, the *dprE1* amplicons were purified using the NucleoSpin® Gel and PCR Clean-up (MACHEREY-NAGEL, Germany). The quantity and purity of the amplicons were measured by UV spectrophotometer (Biotech Epoch™).

Analysis of the *dprE1* gene sequences

Sanger sequencing was performed after DNA amplification to study the sequence of *dprE1* in different clinical isolates. Initially, the purified DNA was mixed with the BigDye™ Terminator v3.1 Ready Reaction Cycle Sequencing Kit (Applied Biosystems, USA) and primers, then processed on the ABI Prism 3730 XL automated sequencer. Then, mutation profiles were investigated by performing DNA alignment of clinical isolates with *M. tuberculosis* H37Rv (GenBank: CP003248.2) as the reference using BioEdit Sequence Alignment version 7.2.5 and the Basic Local Alignment Search Tool (BLAST) server (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>). Structural illustrations of amino acid mutations of DprE1 were generated using PyMOL 3.0 after retrieving the hexagonal crystal structure of *Mycobacterium tuberculosis* *dprE1* (4FEH) from the Protein Data Bank (PDB) (Figure 2).

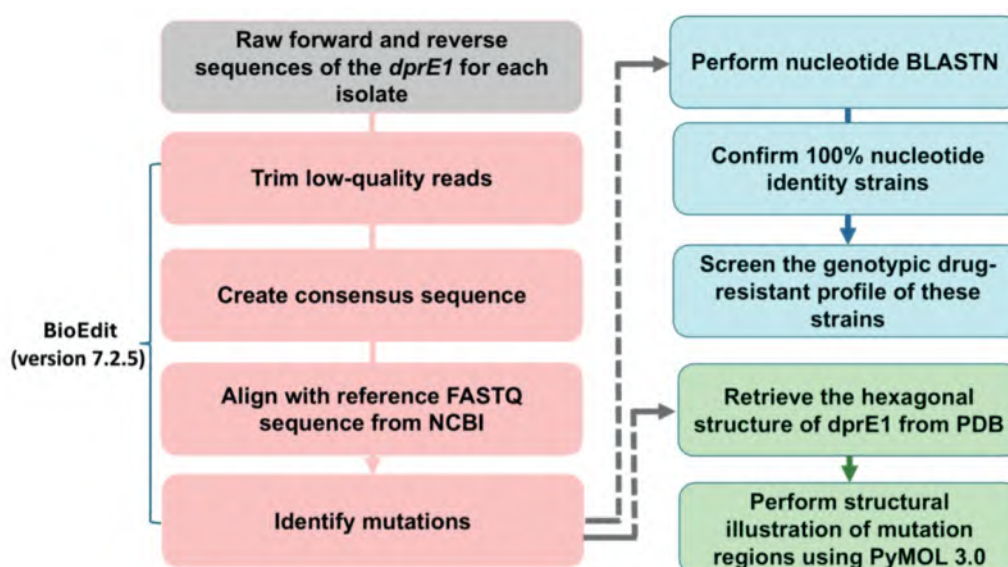


Figure 2. Overview of the sequence analysis workflow.

Result

The genotypic-phenotypic correlation of Mtb clinical isolates

In the agar proportion method, the resistance of Mtb isolates to at least INH and RIF were classified as MDR, isolates resistant only to INH were identified as INH-R, and those resistant to RIF for RIF-R (Table 1, 2, 3). Analysis of the mutation profiles of each isolate revealed that two

MDR isolates (MDR 56 and 57) lacked mutations in INH resistance-associated genes (*inhA* and *katG*), and one RIF-R isolate (51108) was absent of mutations in RIF resistance-associated genes (*rpoB*) (Table 1, 2, 3). However, mutation profiles of the remaining isolates correlated with their DST results.

Table 1. DST and mutation profiles of 11 MDR clinical isolates.

Code strains	DST				Mutation profiles		
	RIF	INH	EMB	SM	<i>rpoB</i>	<i>katG</i>	<i>inhA</i>
MD47	R	R	S	S	D516V	No	T-9C
MD45	R	R	S	S	S522L	S315T	G-17T
MD56	R	R	S	S	H526Y	No	No
MD57	R	R	S	S	S531L	No	No
MD65	R	R	S	R	S531L	S315T	No
sub05	R	R	R	R	S531L	S315T	No
Og43	R	R	S	R	H526Y	S315T	No
Sub10	R	R	S	R	S531L	S315T	No
49030	R	R	S	S	S531L	S315T	No
49753	R	R	S	S	S531L	S315T	No
51268	R	R	S	S	H526D	S315T	No

Note: D516C: substitution of cysteine for aspartic acid of *rpoB* at codon 516, S522L: substitution of leucine for serine of *rpoB* at codon 522, H526Y: substitution of tyrosine for histidine of *rpoB* at codon 526, S531L: substitution of leucine for serine of *rpoB* at codon 531, H526D: substitution of aspartic acid for histidine of *rpoB* at codon 526, S315T: substitution of threonine for serine of *KatG* at codon 315, T-9C: nucleotide change from T to C at *inhA* promoter region (-9), G-17T: nucleotide changes from G to T at *inhA* promoter region (-17), No: no mutation, DST: drug susceptibility testing, R: resistant, S: sensitive, MDR: multi-drug resistance, RIF: Rifampicin, INH: Isoniazid, EMB: Ethambutol, SM: Streptomycin.

Table 2. DST and mutation profiles of 2 INH-R clinical isolates.

Code strains	DST				Mutation profiles		
	RIF	INH	EMB	SM	<i>rpoB</i>	<i>katG</i>	<i>inhA</i>
52200	S	R	S	S	No	No	C-15T
50886	S	R	S	S	No	No	C-15T

Note: C-15T: nucleotide change from C to T at *inhA* promoter region (-15), No: no mutation, DST: drug susceptibility testing, R: resistant, S: sensitive, INH-R: Isoniazid resistance, RIF: Rifampicin, INH: Isoniazid, EMB: Ethambutol, SM: Streptomycin.

Table 3. DST and mutation profiles of 6 RIF-R clinical isolates.

Code strains	DST				Mutation profiles		
	RIF	INH	EMB	SM	<i>rpoB</i>	<i>katG</i>	<i>inhA</i>
R41	R	S	S	S	L511P	No	No
R42	R	S	S	S	L511P	No	No
49698	R	S	S	S	S531L	No	No
49505	R	S	S	S	H526Y	No	No
50071	R	S	S	S	H526Y	No	No
51108	R	S	S	S	No	No	No

Note: L511P: substitution of proline for leucine of *rpoB* at codon 511, S531L: substitution of leucine for serine of *rpoB* at codon 531, H526Y: substitution of tyrosine for histidine of *rpoB* at codon 526. No: no mutation, DST: drug susceptibility testing, R: resistant, S: sensitive, RIF-R: Rifampicin resistance, RIF: Rifampicin, INH: Isoniazid, EMB: Ethambutol, SM: Streptomycin.

PCR amplification of the *dprE1* gene by the specific primers

The specificity of the PCR product of each isolate was demonstrated by agarose gel electrophoresis. The presence of a single band at the expected product size validated the specificity of the primer as presented (Figure 3).

Predominant nucleotide mutation in MDR strains

Sequence analysis of the *dprE1* gene in 19 Mtb isolates was conducted. Among the 11 multidrug-resistant (MDR) isolates, alignment with the reference sequence revealed a nucleotide mutation at codon 459 (C→T) in 9 out of 11 (81.82%) isolates. In contrast, the remaining two MDR

isolates showed no mutations (Figure 4). The mutation at codon 459 led to a synonymous substitution (a mutation that does not change the amino acid sequence) at amino acid position 153. This finding aligns with previous research, where the C→T mutation at this codon was observed in 96 samples from the NCBI database, predominantly from China (13%) and India (28%), especially in drug-resistant Mtb strains.¹⁷ The recurrence of this mutation across diverse geographic regions suggests that it could be part of a broader adaptive response to drug pressure in the global epidemiology of drug-resistant Mtb.

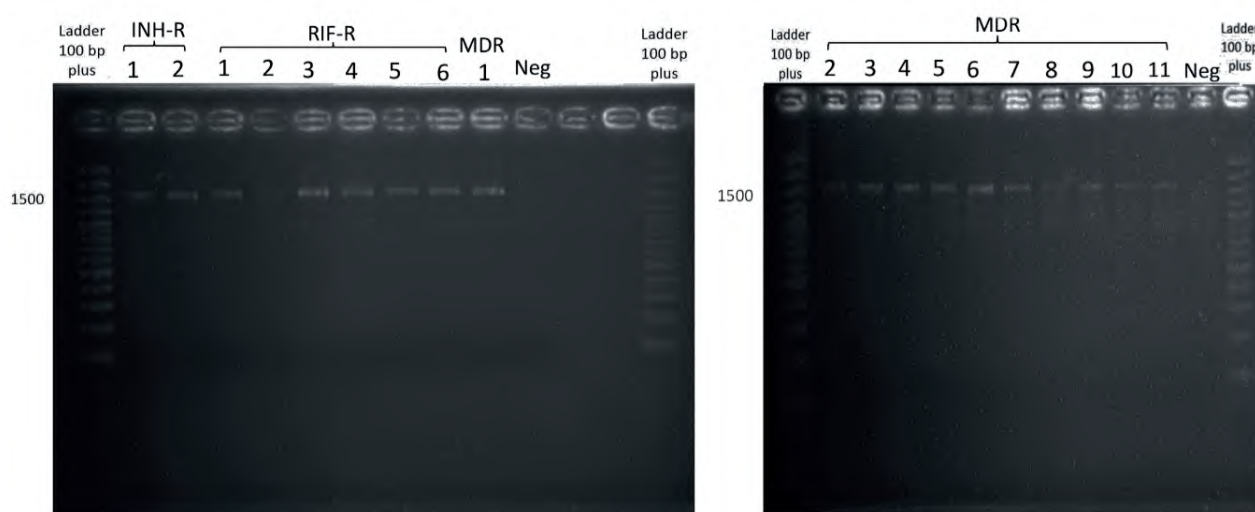


Figure 3. Gel electrophoresis of specific PCR products from 19 clinical isolates.

Sequence alignment of MDR isolates

	450	460	470	480
H37Rv reference	CAGCATGGACCTGCTGACCGCGAGATCCGTCATCTCA			
MD45	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
MD47	CAGCATGGACCTGCTGACCGCGAGATCCGTCATCTCA			
MD56	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
MD57	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
MD65	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
Sub05	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
Sub10	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
Og43	CAGCATGGACCTGCTGACCGCGAGATCCGTCATCTCA			
49030	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
49753	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			
51268	CAGCATGGACCTGCTGACCTGCCGACGGCGAGATCCGTCATCTCA			

*

Figure 4. Sequence alignment of *dprE1* in 11 MDR clinical isolates against the reference sequence from NCBI - *Mycobacterium tuberculosis* H37Rv, CP003248.2 (H37Rv reference). The position of the nucleotide mutation is indicated with *.

One INH-R isolate exhibited the same C→T nucleotide mutation at codon 459 in the mono-resistant isolates, resulting in the same amino acid sequence observed in MDR strains. Another INH-R isolate displayed a G→A mutation at nucleotide position 1066 in the *dprE1* gene, leading to an amino acid substitution of threonine (T) for

alanine (A) at codon 356 (A356T) (Figure 5). BLAST analysis of these sequences against the NCBI database revealed a 100% nucleotide identity of the *dprE1* gene sequences of the 16 DS-Mtb and DR-Mtb strains from various countries in the different geographic regions (Figure 6). Genotypic drug-resistant profiles of all 16 sequence entries were analyzed by screening for mutation in *rpoB*, the *inhA* regulatory region, *inhA*, and *katG* as reported in Table 4.

H37Rv reference
52200
50886

450 460 470 480
 C A G C A T G G A C C T G C T G A C C G C C G A C G G C G A G A T C C G T C A T
 C A G C A T G G A C C T G C T G A C T G C C G A C G G C G A G A T C C G T C A T
 C A G C A T G G A C C T G C T G A C C G C C G A C G G C G A G A T C C G T C A T
 *

1050 1060 1070 1080
 C A A G A A G A T C A T C G G C G T T A T T C A A G C C T C G G G T C A C T A C
 C A A G A A G A T C A T C G G C G T T A T T C A A G C C T C G G G T C A C T A C
 C A A G A A G A T C A T C G G C G T T A T T C A A A C C T C G G G T C A C T A C
 *

330 340 350 360
 G E W N R A Y G P A G F L Q Y Q F V I P T E A V D E F K K I I G V I Q A S G H Y
 G E W N R A Y G P A G F L Q Y Q F V I P T E A V D E F K K I I G V I Q A S G H Y
 G E W N R A Y G P A G F L Q Y Q F V I P T E A V D E F K K I I G V I Q A S G H Y
 *

Figure 5. Sequence alignment of *dprE1* in 2 INH-R clinical isolates against the reference sequence from NCBI - *Mycobacterium tuberculosis* H37Rv, CP003248.2 (H37Rv reference). The position of the nucleotide mutation and amino acid substitution are indicated with *.

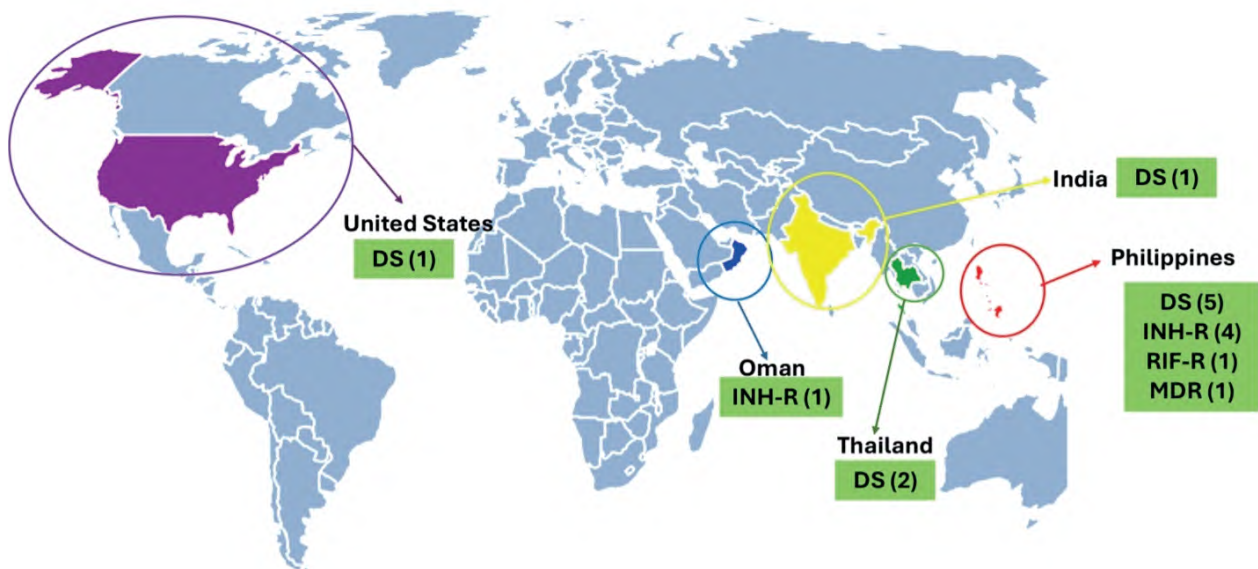


Figure 6. Geographical regions of sixteen samples with a 100% match for the A356T mutation in the INH-R isolate 50886.

Table 4. Locations and drug resistance profiles of *Mtb* strains in the NCBI database with 100% sequence match to *dprE1* of INH-R isolate 50886 (A356T mutation).

Accession	Strain	Location	<i>inhA</i> promoter	<i>inhA</i>	<i>katG</i>	<i>rpoB</i>	Drug resistance profile
CP046308.1	FDAARGOS_751 (Indo-Oceanic T17X)	USA	No	No	R463L	3225 (T→C)	DS
CP029065.1	TBMENG-03	India	No	No	R463L	3225 (T→C)	DS
CP157904.1	H-20-0024	Philippines	G-17T	No	R463L	3225 (T→C)	INH-R
CP157903.1	H-20-0022	Philippines	C-15T	No	R463L	3225 (T→C)	INH-R
CP157905.1	H-21-0019	Philippines	C-15T	No	R463L	3225 (T→C)	INH-R
CP157900.1	H-19-0007	Philippines	No	No	R463L	3225 (T→C)	DS
CP157901.1	H-19-0008	Philippines	No	No	R463L	3225 (T→C)	DS
CP157902.1	H-19-0027	Philippines	No	No	R463L	3225 (T→C)	DS
CP097111.1	MTBCR170020	Thailand	No	No	R463L	3225 (T→C)	DS
CP097110.1	MTBCR170027	Thailand	No	No	R463L	3225 (T→C)	DS
CP130790.1	MTB-Oman-3213318	Oman	C-15T	84 (A→G)	R463L	3225 (T→C)	INH-R
CP040692.1	N0157	Philippines	No	No	R463L	3225 (T→C)	DS
CP069078.1	N0157	Philippines	No	No	R463L	3225 (T→C)	DS
CP009427.1	96121	Philippines	No	S94A	S315T, R463L	3225 (T→C)	INH-R
CP041828.1	3-0090P6C4	Philippines	No	No	R463L	H526S, 3225 (T→C)	RIF-R
CP041827.1	3-0096P6C4	Philippines	C-15T	I21T	R463L	3225 (T→C), S531L	MDR

Note: 3225 (T→C): nucleotide change from T to C in the *rpoB* gene at position 3225, H526S: substitution of serine for histidine of *rpoB* at codon 526, S531L: substitution of leucine for serine of *rpoB* at codon 531, R463L: substitution of leucine for arginine of *katG* at codon 463, S315T: substitution of threonine for serine of *katG* at codon 315, S94A: substitution of alanine for serine of *inhA* at codon 94, I21T: substitution of threonine for isoleucine of *inhA* at codon 21, 84 (A→G): nucleotide changes from A to G in the *inhA* gene at position 84, C-15T: nucleotide change from C to T at *inhA* promoter region (-15), G-17T: nucleotide changes from G to T at *inhA* promoter region (-17), No: no mutation, DS: drug-susceptible strain, INH-R: Isoniazid resistance, RIF-R: Rifampicin resistance, MDR: multi-drug resistance.

For the RIF-R isolates, sequence analysis revealed that two out of six isolates showed no mutations. In comparison, the remaining four isolates carried a mutation at codon 459 (C→T), also found in MDR and INH-R isolates. Interestingly, two of these four RIF-R isolates additionally harbor a G→A mutation at nucleotide position 1198

(G1198A), resulting in an amino acid substitution of isoleucine (I) for valine (V) at codon 400 (V400I) (Figure 7). Notably, no 100% nucleotide identity for this *dprE1* mutant sequence was found in the NCBI database, making this the first uncovering of the V400I amino acid substitution in RIF-R strains.

Sequence alignment of RIF-R isolates

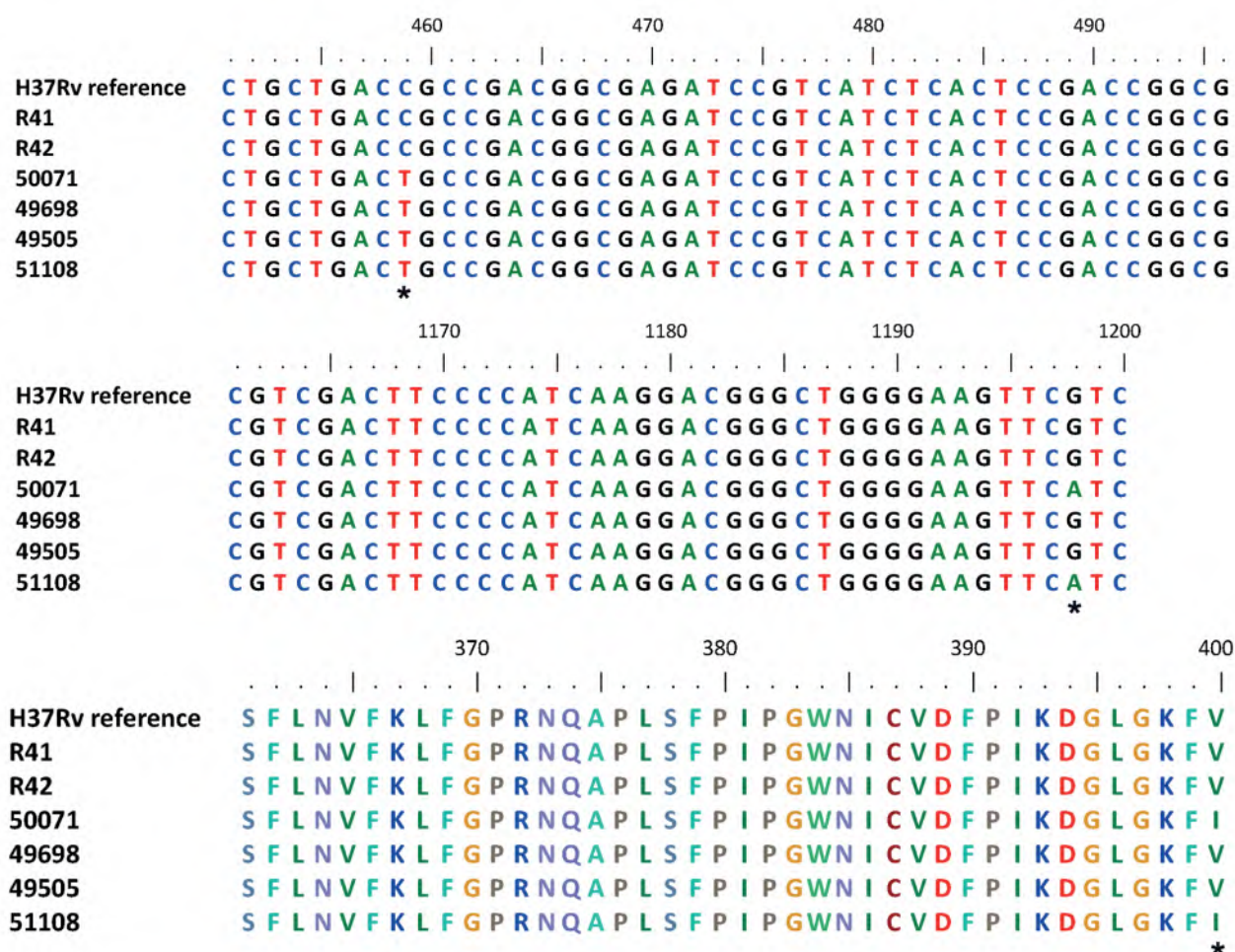


Figure 7. Sequence alignment of *dprE1* in 6 RIF-R clinical isolates against the reference sequence from NCBI - *Mycobacterium tuberculosis* H37Rv, CP003248.2 (H37Rv reference). The position of the nucleotide mutation and amino acid substitution are indicated with *.

The absence of known mutation, the structural impact, and the prevalence of identified mutations

All analyses confirmed that none of the clinical isolates (19/19) had mutations at codon 387 related to BTZ resistance, suggesting all isolates might be susceptible to BTZ compounds. The absence of BTZ resistance-related mutations is particularly significant, as it indicates the continued efficacy of BTZ compounds against these clinical isolates, offering a potential therapeutic option. However, the C→T nucleotide mutation at codon 459 emerged as the most frequently detected mutation, occurring in 14 out of 19 isolates. Consequently, this mutation can be recognized as a common genetic polymorphism across all drug-resistant profiles (73.68%), including 9 MDR strains,

1 INH-R strain, and 4 RIF-R strains, thereby broadening its significance in the context of TB resistance (Figure 8). To study the potential impact of the mutations that were found in INH-R and RIF-R isolates, the amino acid mutation codons were mapped onto the hexagonal crystal structure of the Mtb DprE1 enzyme (PDB ID: 4FEH), obtained from the Protein Data Bank (PDB). Protein structure analysis revealed that both amino acid mutations in INH-R (A356T) and RIF-R (V400I) occur within the substrate/inhibitor-binding domain of the DprE1 enzyme (amino acid residues 197-412) (Figure 9). This suggests the significance of this mutation, which can potentially impact the interaction with the inhibitor binding efficiency.

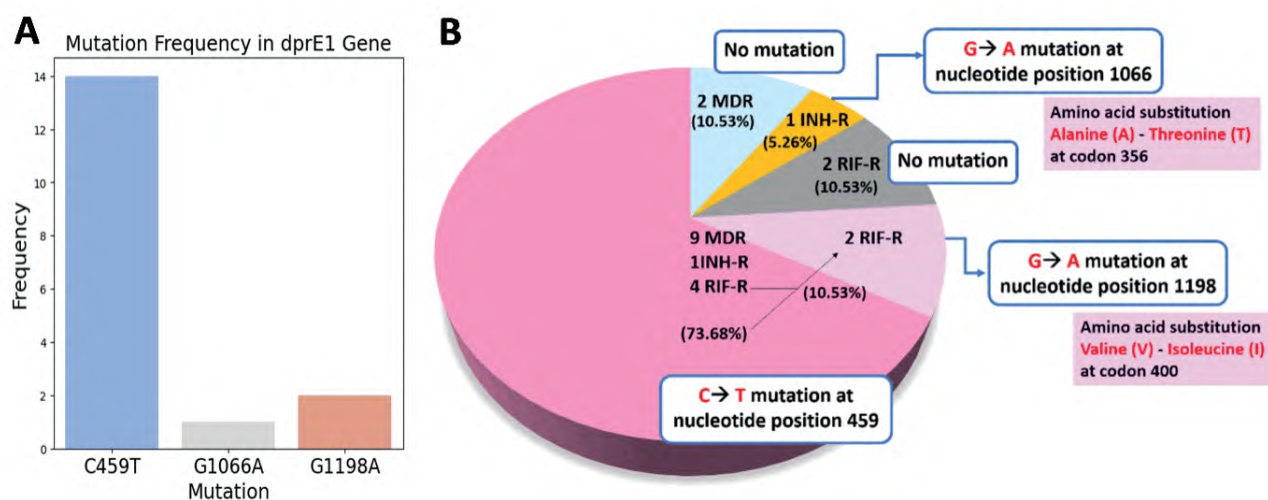


Figure 8. Summary of mutation frequency and distribution of the gene across 19 Mtb clinical isolates. **A:** The bar chart indicated the mutation frequencies of C459T, G1066A, and G1198A nucleotide positions. **B:** The pie chart demonstrated the distribution of mutation patterns among MDR, INH-R and RIF-R clinical isolates, highlighting the nucleotide mutations and their corresponding amino acid substitutions.

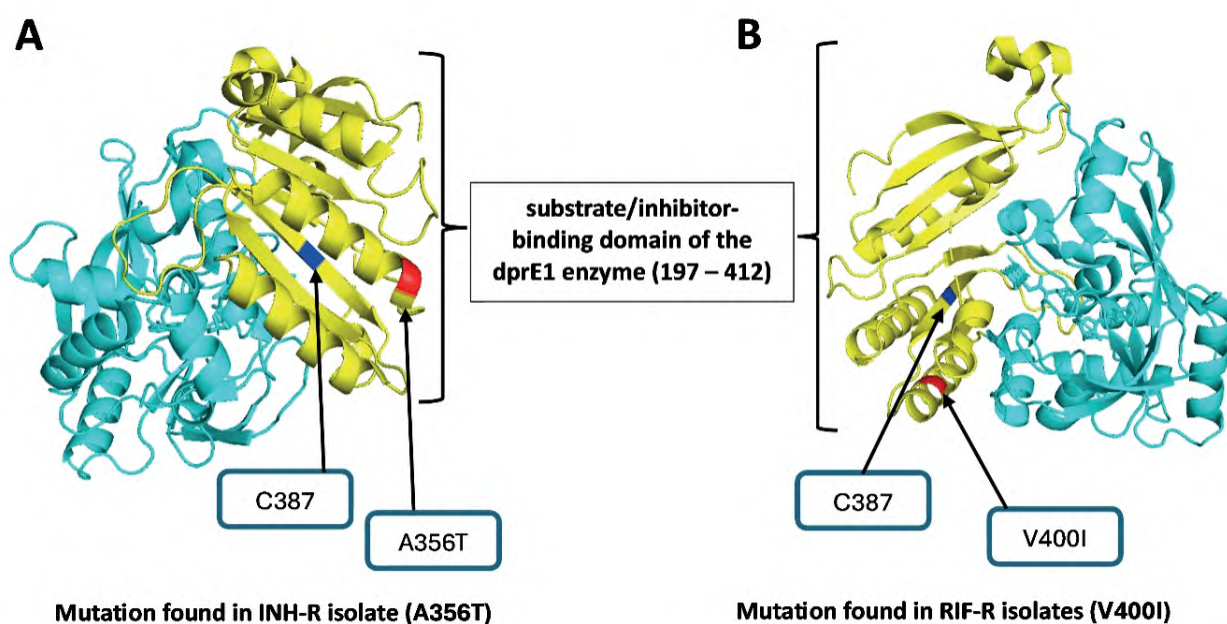


Figure 9. Structural illustrations of amino acid substitutions in the dprE1 enzyme. **(A)** A356T amino acid mutation was identified in an INH-R isolate. **(B)** V400I amino acid mutation was identified in RIF-R isolates. Cysteine 387 residue (C387) was highlighted to indicate a known mutation region associated with resistance to BTZ compounds. The yellow region (amino acid residues 197–412) represents the substrate/inhibitor binding sites of the dprE1 enzyme.

Discussion

In recent years, whole-cell screening has identified several new drug families that target essential proteins involved in cell wall component construction.¹⁸ While cell wall targeting drugs like isoniazid and ethambutol are effective against drug-sensitive Mtb, treating MDR Mtb strains remains a significant challenge, as these strains have developed resistance to the first-line drugs.¹⁹ The discovery of DprE1, due to its essential role of involvement in the fundamental synthesis processes of LAM and AG and

its localization in epimerization processes, identifies it as a valuable cell wall target for MDR-TB. It was demonstrated that silencing of DprE1 caused significant growth arrest, swelling of the bacteria, and cell wall lysis.²⁰ Among the covalent inhibitors of DprE1, the benzothiazinones BTZ043 and PBTZ169 stand out as the most effective compounds, which are currently advancing through phase II clinical trials.²¹ However, mutations in the drug target genes usually confer high resistance to antibiotics.²² A point mutation of a cysteine residue at codon 387 in DprE1 has

been associated with resistance to BTZ compounds in *Mtb*, presenting a challenge to the effectiveness of these promising inhibitors.⁷

Therefore, it is crucial to investigate mutations in the *dprE1* gene, particularly in drug-resistant strains such as MDR-TB, to elucidate potential resistance mechanisms and provide critical information that could enhance the effectiveness of these drugs. However, there needs to be more reports on the sequence analysis and identification of mutations in the *dprE1* gene associated with these promising drugs. In the present study, we focused on the genetic analysis of the *dprE1* gene in various drug-resistant clinical isolates, with particular emphasis on MDR-TB. As expected, no mutations were found at the codon 387 in any of the 19 isolates. This suggests that the present drug-resistant strains remain susceptible to BTZ compounds, which inhibit DprE1 by forming a covalent adduct with this residue. This finding aligns with recent reports from different geographical regions, which showed no mutation of *dprE1* in clinical isolates.¹⁵ Surprisingly, 14 out of 19 isolates show the same nucleotide mutation (C→T) in our work, and this sequence was 100% matched with the sequences from NCBI, mostly in drug-resistant strains. Recent work has also identified this mutation in DS strains, suggesting it might be a genetic polymorphism rather than drug resistance-related.¹⁷ However, investigating its impact on gene expression will be valuable, as silent mutations, although they do not alter the amino acid sequence, can still affect mRNA stability and translation efficiency, potentially influencing treatment response.²³

Noncovalent inhibitors also target the active site of the DprE1 enzyme, but their activity does not rely on the presence of cysteine.²⁴ Beyond covalent bond formation, studies have shown that the DprE1 enzyme can also be inhibited through hydrophobic interactions, such as at residue 275 by the binding of selamectin.^{25,26} TCA1 is a noncovalent inhibitor that does not possess the nitro group required for covalent binding to codon 387. Interestingly, a DprE1 mutation with a Y314C substitution, which confers resistance to TCA1, has been found to remain sensitive to BTZ. This suggests that TCA1 likely interacts with DprE1 through a mechanism different from BTZ.^{10,18} Moreover, earlier work demonstrated that mutation of the 16S rRNA gene at positions 1401, 1402, and 1484 is associated with cross-resistance between Amikacin, Kanamycin, and Capreomycin in *Mtb*.²⁷ These all highlight that other residues within DprE1 are also crucial for interactions with inhibitors, and mutation of these residues might potentially develop drug resistance.

Our study identified nucleotide mutations that led to amino acid substitutions in one INH-R (A356T) and two RIF-R (V400I) isolates. Although these mutations do not correspond to previously identified resistance sites for either covalent or noncovalent inhibitors, they are located within the substrate/inhibitor binding domain of DprE1. This domain is essential for the enzyme's function, and mutations within it could alter the enzyme's interaction with substrates or inhibitors, potentially contributing to the development of drug resistance. When the mutation

sequences were analyzed using the NCBI database, it was found that sixteen *Mtb* strains from different regions showed a 100% identity with the *dprE1* mutant sequences in an INH-resistant isolate. These specific mutations are common and have been identified in various geographical locations, suggesting widespread occurrence potentially driven by clonal expansion through migration or selective antibiotic pressure in regions with high drug use. In addition, this mutation was also observed in DS strains, and it could pose a threat to treatment if it is related to drug resistance.

In contrast, no 100% matches were found for the sequences from the RIF-resistant isolates. This absence of exact matches highlights that the mutations present in the RIF-resistant strains might represent novel or less well-characterized genetic variations. Therefore, deeper investigation into these mutations is necessary to determine how they might affect the overall resistance profile of the isolates.

An interesting finding is that amino acid substitutions in DprE1 were predominantly observed in both INH-resistant (INH-R) and RIF-resistant (RIF-R) isolates. Since *Mtb* does not acquire resistance through horizontal gene transfer, the evolution of multi-drug resistance is influenced by pre-existing drug resistance.²⁸ Previous reports indicate that strains with an isoniazid mono-resistant background have a 15-fold higher risk of developing rifampicin resistance than wild-type strains. This suggests that DprE1 mutations may arise from subsequent mutations in mono-resistant strains.²⁹ Further research should focus on mono-resistant isolates to elucidate the mechanisms driving these additional mutations.

Limitation

This study was conducted on a limited number of clinical isolates, and larger sample sizes are needed for a comprehensive understanding of the mutation patterns in the *dprE1* gene. Furthermore, the isolates investigated in this study were collected exclusively from northern Thailand, which may not fully represent the different mutations that might be prevalent in other regions. Functional studies of the amino acid changes in these strains will be necessary to understand their susceptibility to the proposed drugs.

Conclusion

This research revealed that Cys387 mutation was not observed in the drug-resistant isolates, supporting the positive impact of BTZ compounds in eradicating MDR. While a common synonymous substitution was identified in several isolates, its presence in drug-sensitive strains suggests a potential genetic polymorphism. However, detecting non-synonymous substitution in different residues of INH-R and RIF-R isolates indicates that current circulating mono resistance strains can acquire additional mutations in *dprE1* genes. These amino acid changes in the inhibitor binding domain could alter drug interaction, underscoring the need for further investigation to determine their impact on treatment efficacy.

Conflicts of interest

The authors declare no conflict of interest.

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References

- [1] Bagcchi S. WHO's Global Tuberculosis Report 2022. *Lancet Microbe*. 2023; 4(1): e20. doi: 10.1016/S2666-5247(22)00359-7
- [2] Dash S, Rath E, Kumar A, Chawla K, Kini SG. Identification of DprE1 inhibitors for tuberculosis through integrated in-silico approaches. *Sci Rep*. 2024; 14(1): 11315. doi: 10.1038/s41598-024-61901-x
- [3] de Steenwinkel JE, ten Kate MT, de Knecht GJ, Verbrugh HA, Aarnoutse RE, Boeree MJ, et al. Consequences of noncompliance for therapy efficacy and emergence of resistance in murine tuberculosis caused by the Beijing genotype of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2012; 56(9): 4937-44. doi: 10.1128/AAC.00124-12
- [4] Dash S, Rath E, Kumar A, Chawla K, Joseph A, Kini SG. Structure-activity relationship mediated molecular insights of DprE1 inhibitors: A Comprehensive Review. *J Biomol Struct Dyn*. 2024; 42(12): 6472-522. doi: 10.1080/07391102.2023.2230312
- [5] Gandhi NR, Nunn P, Dheda K, Schaaf HS, Zignol M, van Soolingen D, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet*. 2010; 375(9728): 1830-43. doi: 10.1016/S0140-6736(10)60410-2
- [6] Jacobo-Delgado YM, Rodríguez-Carlos A, Serrano CJ, Rivas-Santiago B. *Mycobacterium tuberculosis* cell-wall and antimicrobial peptides: a mission impossible? *Front Immunol*. 2023; 14:1194923. doi: 10.3389/fimmu.2023.1194923
- [7] Riccardi G, Pasca MR, Chiarelli LR, Manina G, Mattevi A, Binda C. The DprE1 enzyme, one of the most vulnerable targets of *Mycobacterium tuberculosis*. *Appl Microbiol Biotechnol*. 2013; 97(20): 8841-8. doi: 10.1007/s00253-013-5218-x
- [8] Chen K, Xu R, Hu X, Li D, Hou T, Kang Y. Recent advances in the development of DprE1 inhibitors using AI/CADD approaches. *Drug Discov Today*. 2024;29(6):103987. doi: 10.1016/j.drudis.2024.103987
- [9] Brennan PJ, Nikaido H. The envelope of mycobacteria. *Annu Rev Biochem*. 1995; 64: 29-63. doi: 10.1146/annurev.bi.64.070195.000333
- [10] Piton J, Foo CS, Cole ST. Structural studies of *Mycobacterium tuberculosis* DprE1 interacting with its inhibitors. *Drug Discov Today*. 2017; 22(3): 526-33. doi: 10.1016/j.drudis.2016.09.014
- [11] Yadav S, Soni A, Tanwar O, Bhadane R, Besra GS, Kawathekar N. DprE1 Inhibitors: Enduring aspirations for future antituberculosis drug discovery. *ChemMedChem*. 2023; 18(16): e202300099. doi: 10.1002/cmdc.202300099
- [12] Shi J, Lu J, Wen S, Zong Z, Huo F, Luo J, et al. In Vitro Activity of PBTZ169 against multiple *Mycobacterium* species. *Antimicrob Agents Chemother*. 2018; 62(11): e01314-18. doi: 10.1128/AAC.01314-18
- [13] Fil M, Alibert S. Unveiling DprE1 as a Key Target in the Fight against Tuberculosis: Insights and perspectives on developing novel antimicrobial agents. *BioMed*. 2024; 4(3): 220-36. doi: 10.3390/biomed4030018
- [14] Incandela ML, Perrin E, Fondi M, de Jesus Lopes Ribeiro AL, Mori G, Moiana A, et al. DprE1, a new taxonomic marker in mycobacteria. *FEMS Microbiol Lett*. 2013; 348(1): 66-73. doi: 10.1111/1574-6968.12246
- [15] Pasca MR, Degiacomi G, Ribeiro AL, Zara F, De Mori P, Heym B, et al. Clinical isolates of *Mycobacterium tuberculosis* in four European hospitals are uniformly susceptible to benzothiazinones. *Antimicrob Agents Chemother*. 2010; 54(4): 1616-8. doi: 10.1128/AAC.01676-09
- [16] Saikaew S, Thongprachum A, Pongsararuk R, Thanraka A, Kunyanone N, Chaiyasirinroje B, et al. Genotypic distribution and the epidemiology of multidrug resistant tuberculosis in Upper Northern Thailand. *Antibiotics (Basel)*. 2022; 11(12): 1733. doi: 10.3390/antibiotics11121733
- [17] Yimcharoen M, Saikaew S, Wattananandkul U, Phunpae P, Intorasoot S, Kasinrerk W, et al. The regulation of ManLAM-related gene expression in *Mycobacterium tuberculosis* with different drug resistance profiles following isoniazid treatment. *Infect Drug Resist*. 2022; 15: 399-412. doi: 10.2147/IDR.S346869
- [18] Amado PSM, Woodley C, Cristiano MLS, O'Neill PM. Recent advances of DprE1 inhibitors against *Mycobacterium tuberculosis*: Computational analysis of physicochemical and ADMET properties. *ACS Omega*. 2022; 7(45): 40659-81. doi: 10.1021/acsomega.2c05307
- [19] Yadav P. Challenges & solutions for recent advancements in multi-drugs resistance tuberculosis: A Review. *Microbiol Insights*. 2023; 16: 11786361231152438. doi: 10.1177/11786361231152438
- [20] Kolly GS, Boldrin F, Sala C, Dhar N, Hartkoorn RC, Ventura M, et al. Assessing the essentiality of the decaprenylphospho-d-arabinofuranose pathway in *Mycobacterium tuberculosis* using conditional mutants. *Mol Microbiol*. 2014; 92(1): 194-211. doi: 10.1111/mmi.12546
- [21] Poulton NC, Azadian ZA, DeJesus MA, Rock JM. Mutations in rv0678 confer low-level resistance to benzothiazinone DprE1 inhibitors in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2022; 66(9): e0090422. doi: 10.1128/aac.00904-22
- [22] Gygli SM, Borrell S, Trauner A, Gagneux S. Antimicrobial

- resistance in *Mycobacterium tuberculosis*: mechanistic and evolutionary perspectives. FEMS Microbiol Rev. 2017; 41(3): 354-73. doi: 10.1093/femsre/fux011
- [23] Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, et al. A “silent” polymorphism in the MDR1 gene changes substrate specificity. Science. 2007; 315(5811): 525-8. doi: 10.1126/science.1135308
- [24] Finger V, Kucera T, Kafkova R, Muckova L, Dolezal R, Kubes J, et al. 2,6-Disubstituted 7-(naphthalen-2-yl-methyl)-7H-purines as a new class of potent antitubercular agents inhibiting DprE1. Eur J Med Chem. 2023; 258: 115611. doi: 10.1016/j.ejmech.2023.115611
- [25] Ezquerro-Aznárez JM, Degiacomi G, Gašparovič H, Stelitano G, Sammartino JC, Korduláková J, et al. The veterinary anti-parasitic selamectin is a novel inhibitor of the *Mycobacterium tuberculosis* DprE1 Enzyme. Int J Mol Sci. 2022; 23(2): 771. doi: 10.3390/ijms23020771
- [26] Makarov V, Manina G, Mikusova K, Möllmann U, Ryabova O, Saint-Joanis B, et al. Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. Science. 2009; 324(5928): 801-4. doi: 10.1126/science.1171583
- [27] Jugheli L, Bzekalava N, de Rijk P, Fissette K, Portaels F, Rigouts L. High level of cross-resistance between kanamycin, amikacin, and capreomycin among *Mycobacterium tuberculosis* isolates from Georgia and a close relation with mutations in the rrs gene. Antimicrob Agents Chemother. 2009; 53(12): 5064-8. doi: 10.1128/AAC.00851-09
- [28] Bergval I, Kwok B, Schuitema A, Kremer K, van Soolingen D, Klatser P, et al. Pre-existing isoniazid resistance, but not the genotype of *Mycobacterium tuberculosis* drives rifampicin resistance codon preference in vitro. PLoS One. 2012; 7(1): e29108. doi: 10.1371/journal.pone.0029108
- [29] Torres Ortiz A, Coronel J, Vidal JR, Bonilla C, Moore DAJ, Gilman RH, et al. Genomic signatures of pre-resistance in *Mycobacterium tuberculosis*. Nat Commun. 2021; 12(1): 7312. doi: 10.1038/s41467-021-27616-7

Assessment of dose uniformity and optimal CT number for virtual bolus in breast VMAT planning

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ABSTRACT

Background: ICRU Report No. 83 proposes using the Flash Region in the strategic design of breast cancer treatment. However, concerns persist regarding the delivery of the designated radiation dose to breast cancer patients undergoing Volumetric Modulated Arc Therapy (VMAT) with virtual bolus in the irradiation plan.

Objective: This study aimed to assess dose uniformity in breast VMAT treatment with a virtual bolus, validate the planning dose by comparing it with nanoDot™ measurements on a Rando phantom, and determine the optimal CT number for the virtual bolus in breast VMAT planning.

Materials and methods: To assess dose uniformity in the breast VMAT plan, nine nanoDot™ dosimeters were placed on the breast of Rando phantom, followed by CT simulation and VMAT treatment planning. The clinical target volume (CTV) and organs at risk were contoured, and the planning target volume (PTV) boundaries were expanded by 5 mm and 10 mm for virtual bolus thicknesses of 10 mm and 15 mm, respectively. The CT number of the virtual bolus varied from 0 to -700 HU. The planning doses at 9 points were determined, and the coefficient of variation (%CV) was calculated. Additionally, measurements at these 9 points were performed using nanoDot™ dosimeters. The calculated and measured doses were then compared. Finally, VMAT treatment plans with a virtual bolus were implemented in 10 breast cancer patients, using the virtual bolus with varying CT numbers as in the phantom study to evaluate the optimal CT number of the bolus.

Results: The doses among the 9 points for each plan were uniform, with a %CV of less than 4. For calculated dose validation, the percentage differences between the measured and calculated dose for all treatment plans, with variations in the CT number and the bolus thickness, were within $\pm 5\%$. To determine the optimal CT number for the virtual bolus, the breast cancer treatment plan that met the dose criteria for tumors and organs at risk was the plan with a CT number of 0 HU for both virtual bolus thicknesses of 10 and 15 mm.

Conclusion: Virtual bolus provides uniform dose distribution for breast VMAT planning, which measurements from nanoDot™ can validate. The appropriate CT number for the virtual bolus is 0 HU for both bolus thicknesses. In future studies, measurements should be conducted on actual patients.

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Introduction

For breast cancer, treatment will vary depending on the stage and type of cancer. Several treatment techniques

are used for breast cancer, including Three-dimensional conformal radiation therapy (3D-CRT), Intensity-modulated radiation therapy (IMRT), and Volumetric modulated arc therapy (VMAT). The VMAT technique may increase the risk of second cancers and other complications due to the low dose of radiation that the patient receives.^{1,2} This emphasizes the importance of carefully choosing VMAT irradiation. Therefore, in patients with breast cancer, this technique is primarily employed in highly complex cases, as planning treatment according to dose constraints using standard techniques is not possible.¹ VMAT was found to spare radiation doses to the heart, lungs, and breast on the opposite side better than the 3D field in the field.³

According to ICRU report No. 83, the Flash region is recommended for treatment planning⁴ because the breast is in the area affected by breathing movement, leading to potential anatomical changes such as edema and uncertainty in patient positioning.⁵ The study found that incorporating virtual bolus in VMAT did not affect radiation dose. Yet, it resulted in a more favorable distribution of radiation doses in anatomically changing visual data than calculations without virtual bolus. This led to the conclusion that the use of virtual bolus was both safe and helpful in compensating for breast changes that may occur during irradiation.⁶

When performing the treatment plan with IMRT, a tool known as Skin Flash (Eclipse treatment planning system, Varian Medical Systems, Palo Alto, CA) is employed. Skin flash refers to a method where an intentional margin of the treatment field is extended beyond the skin surface to ensure the skin receives the required dose. However, for VMAT, since Skin Flash is unavailable, virtual bolus is used as an alternative option. This technique electronically applies a virtual bolus to the skin surface within the treatment planning system to achieve the desired dose distribution.

The nanoDot™ (Landauer Inc., Glenwood, IL, USA) is an optically stimulated luminescent dosimeter (OSLD) generally used in point dosimetry for radiation therapy applications.⁷⁻¹² It is employed for dosimetry to determine organ doses during irradiation, such as skin¹³⁻¹⁶ and eye lens.¹⁷ The nanoDot™ offers several benefits, including its tiny size and repeatable readout, making it a preferred alternative for in vivo dosimetry.^{17,18} This study selected nanoDot™ to measure the breast dose compared with treatment planning.

A previous study by Lizondo *et al.* optimized virtual bolus thickness and HU values in VMAT for breast radiotherapy.¹ They found that this could improve

the efficacy of pseudo skin flash, thereby enhancing treatment precision. However, this study did not compare the results with actual measurements. To the best of our knowledge, limited research exists regarding the planning doses for breast cancer in the flash region compared to measurements. Therefore, this study aims to assess dose uniformity in breast VMAT treatment with a virtual bolus and validate it by comparing radiation doses between breast VMAT treatment planning (utilizing virtual bolus) and nanoDot™ measurements in breast treatments performed on the Rando phantom. Additionally, we seek to assess the appropriate CT number for the virtual bolus in the breast VMAT treatment plan and compare the radiation doses received by tumors and organs at risk during breast VMAT (virtual bolus) treatment planning for breast cancer patients.

Materials and methods

This ethical research was approved by the Naresuan University IRB (IRB No. P1-0163/2565) and the ethical committee of Chanthaburi Province (COA No. 022/66). To achieve the objectives, we experimented with two steps. The first step involved evaluating dose uniformity and validating the doses from breast VMAT treatment planning with measurements from nanoDot™. For the second step, the optimal CT number of the virtual bolus was evaluated in clinical breast VMAT plans.

Assessment of dose uniformity for a virtual bolus in breast VMAT planning and validation with nanoDot™ measurement: Phantom study

Computed tomography simulation

Nine nanoDot™ dosimeters were positioned on the left breast of the female Alderson RANDO phantom (RSD Radiology Support Devices, CA, USA) with the 5 cm separation between two neighboring (Figure 1a), to determine the position of nanoDot™ in the treatment planning (not for dose measurement). Then, a bolus with a thickness of 1.5 cm was placed over the nanoDot™ detectors covering the left breast to maintain a charged particle equilibrium in the measurement, as shown in Figure 1 (b); this physical bolus represented the breast tissue of the phantom. Subsequently, a scan was conducted using the Brilliance Big Bore computed tomography (CT) simulator (Philips, Amsterdam, the Netherlands) with a slice thickness of 3 mm, 120 kVp, and 140 mAs. The set-up position is presented in Figure 2. Then, CT images were transferred to a computerized treatment planning system.

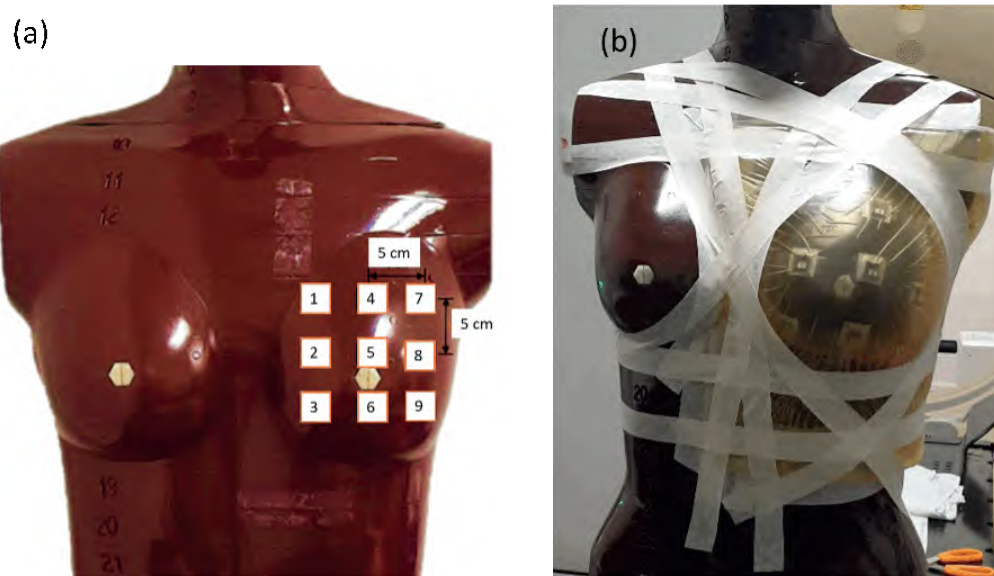


Figure 1. The nanoDot™ dosimeter settings with the Rando phantom show the position of the nanoDot™ dosimeters (a) and 1.5 cm of bolus covering the left breast (b).



Figure 2. Phantom setup during CT simulation.

Treatment planning

The left breast (planning target volume; PTV) was delineated with the boundary covering the skin of the physical bolus, as observed in the CT image (Image Set 1, representing no virtual bolus). Subsequently, two additional sets of image data were generated by extending the tumor boundaries beyond the front torso by 5 mm and 10 mm, respectively, as illustrated in Figure 3. According to the Eclipse™ treatment planning system version 16.01.10

(Varian Medical Systems, CA, USA) instruction, creating a bolus that covers the extended target volume with at least a 3 mm margin is recommended. This was done to develop virtual boluses with thicknesses of 10 mm (PTV +5 mm) and 15 mm (PTV+10 mm). Consequently, there are three datasets: no virtual bolus, 10-mm virtual bolus, and 15-mm virtual bolus. The CT number of the bolus was adjusted from 0 to -700 HU in 100 HU decrements for each CT image dataset.

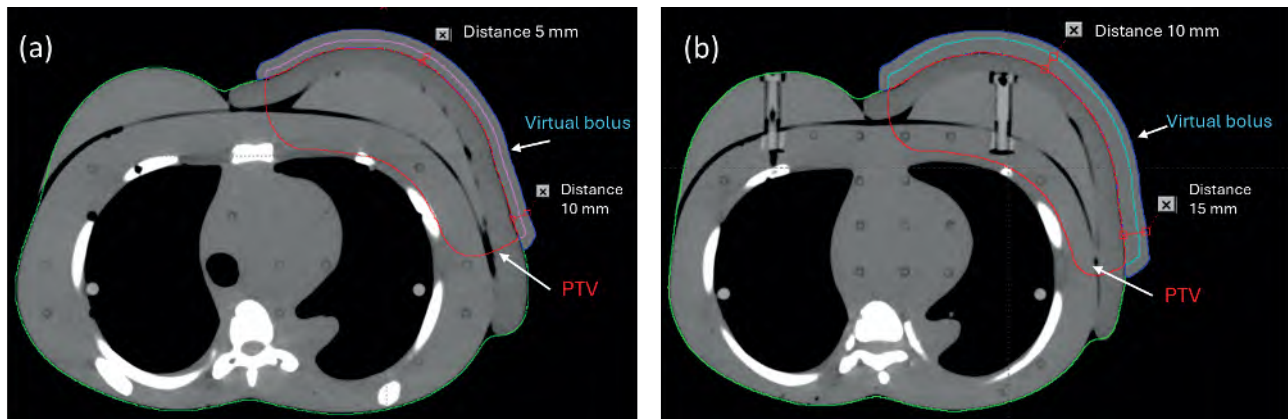


Figure 3. Delineation of the PTV (red line) and virtual bolus (blue line) creation.
a: CT image of 10-mm virtual bolus (PTV +5mm) (a), b: CT image of 15-mm virtual bolus PTV+10 mm.

After establishing the treatment plan, the virtual tissue equivalent material was removed, and the radiation dose was recalculated. The number of fractions was changed to 1. Subsequently, the doses at all 9 locations from the treatment plan, corresponding to the positions of the nanoDot™, were recorded for comparison with the measurement data.

The treatment plans with VMAT technique were generated for these 3 image sets using the Eclipse™ treatment planning system version 16.01.10, employing 6 MV energy and assigning a total dose of 50 Gy in 2 Gy

per fraction for 25 sessions. For planning criteria, the maximum dose (D_{max}) received did not exceed 115% of the prescribed dose or 57.5 Gy, and the dose to 95% of the volume ($D_{95\%}$) received was not less than 95% of the prescribed dose or not less than 47.5 Gy. The example of dose distribution is illustrated in Figure 4.

The treatment plans were replanned by adjusting the CT number of the tissue equivalent material to all HU settings for 2 bolus thicknesses and re-optimization with the new CT number.

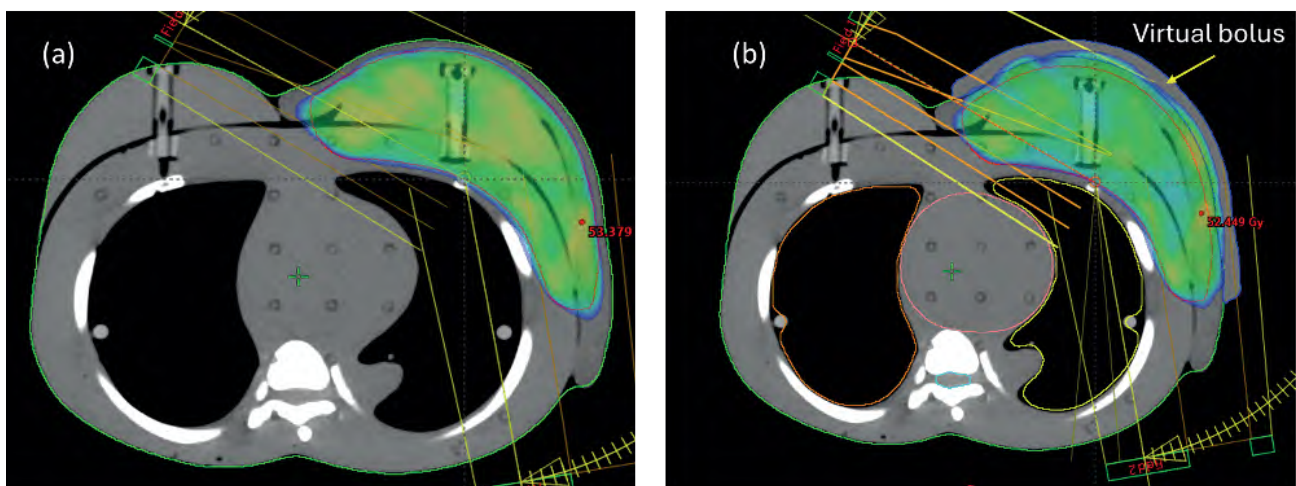


Figure 4. Treatment plan in Rando Phantom. a: no virtual bolus, b: with virtual bolus.

The nanoDot™ dose measurement

Determination of sensitivity correction factor of nanoDot™

The nanoDot™ sensitivity correction factor addresses the adjustments required for error readings among detectors within a given batch. While it is ideal for all detectors to provide identical dose measurements, individual detectors might display variations in sensitivity. To address these differences, a correction factor called the “sensitivity correction factor” (k_{sen}) was applied.

The correction factor for each nanoDot™ was computed by establishing the ratio between the average reading obtained from all detectors in the same batch (M_{avg} in cGy) and its specific reading (M in cGy), as demonstrated in Equation 1.

$$k_{\text{sen}} = \frac{M_{\text{avg}}}{M} \quad (1)$$

For the determination of the sensitivity correction factor, a total of 100 nanoDot™ detectors underwent irradiation with a 100 cGy dose of a 6MV X-ray beam, where the irradiation setup included a source-to-axis distance (SAD) of 100 cm, a depth of 10 cm, and a field size (FS) of 20x20 cm². The Clinac 2100 linear accelerator (Varian Medical Systems in Palo Alto, CA, USA) was employed for this study. Subsequently, Equation 1 was utilized to calculate the sensitivity correction factor for each nanoDot™. The nanoDot™ detectors exhibiting a sensitivity correction factor beyond $\pm 5\%$ were excluded, and only those with sensitivities close to 1 were included in the subsequent experiment.

Calibration of nanoDot™

For the calibration of nanoDot™ dosimeters, 3 out of the 100 detectors in the batch were selected, ensuring their sensitivity did not vary by more than $\pm 5\%$. These 3 nanoDot™ dosimeters were calibrated by comparing it with an ionization chamber (IC) of 0.65 cm³ volume (Wellhofer FC65-G IBA Dosimetry, Schwarzenbruck, Germany), irradiating with 6 MV X-rays at a dose of 100 cGy, a dose rate of 400 MU/min, a field size of 10 x 10 cm², source-to-axis distance (SAD) of 100 cm, and a depth of 1.5 cm. The VitalBeam linear accelerator (Varian Medical Systems, CA, USA) was employed for this study. The sensitivity of each dosimeter was corrected, and the nanoDot™ calibration factor was determined using Equation 2.

$$\text{Calibration factor (CF)} = \frac{D_{\text{IC}}}{M_{\text{OSLD}}} \quad (2)$$

where, D_{IC} is radiation dose measured by IC (cGy) according to the recommendation of TRS 398¹⁹ and M_{OSLD} is the nanoDot reading with the correction of sensitivity (cGy).

Measurement

All planned treatment sessions measured the radiation dose in the nanoDot™. The radiation doses in the treatment plan were evaluated by comparing the measurements using nanoDot™ dosimeters. The background nanoDot™ readings were removed from the reading, and the readings were

corrected for sensitivity. The calibration factor was then applied according to equation 3. The nanoDot™ measurements were repeated three times, and the results were averaged for each measurement point. Then, the percentage difference between calculated and measured doses was assessed to confirm the planning dose with the measurement.

$$D_{\text{OSLD}} = M_{\text{OSLD}} \times CF \quad (3)$$

where, M_{OSLD} is the nanoDot™ reading corrected for k_{sen} and CF is the calibration factor of nanoDot™.

The comparison of mean calculated and measured doses in terms of percentage dose difference could confirm the reliability of the doses calculated with the virtual bolus, ensuring that the dose distribution covered the entire breast by calculating the coefficient of variance (%CV). The following experiment aimed to determine the optimal CT number for the virtual bolus in VMAT plan applications for various breast cancer cases.

Determination of optimal CT number of virtual bolus: Clinical study

Ten sets of CT images from breast cancer patients were included in this study. The inclusion criteria were the VMAT plans of breast cancer patients with left breast. The left breast patient was chosen because we would like to evaluate the dose for the heart. For each patient, three CT images were studied, representing no virtual bolus, a 10-mm virtual bolus, and a 15-mm virtual bolus. The CT numbers were varied from 0 to -700 HU in 100 HU decrements. A treatment plan was then executed on a series of CT images of left breast cancer patients, with the treatment plan and adjustment parameters being identical to those used in the phantom study. The maximum dose (D_{max}) received was at most 115% of the specified dose or 57.5 Gy, and the dose to 95% of the volume ($D_{95\%}$) received was not less than 95% of the prescribed dose or not less than 47.5 Gy.

Equations 4 and 5 were used to determine the conformity number (CN)²⁰ and homogeneity index (HI)⁴, respectively.

$$CN = \frac{TV_{\text{RI}}}{TV} \times \frac{TV_{\text{RI}}}{V_{\text{RI}}} \quad (4)$$

where, TV_{RI} is the target volume covered by the reference isodose, TV is the target volume, and V_{RI} is the volume of the reference isodose.

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (5)$$

where $D_{2\%}$, $D_{50\%}$, and $D_{98\%}$ are the doses to 2%, 50%, and 98% of the target volume, respectively. The range of CN is 0 to 1, with the ideal value equal to 1. The HI should be close to 0 to indicate homogeneity.

The radiation doses in high-risk organs were compared, considering D_{mean} and $V_{35\%}$ for the heart and $V_{55\%}$ for the lungs, regarding specific limits outlined in RTOG 1005.²¹ This comparison aided in determining the CT number of

the virtual tissue equivalent material suitable for planning treatment with this technique.

Results

Sensitivity correction factor of nanoDot™

The sensitivity correction factor of nanoDot™ was in the range of 0.952-1.072. The nanoDot™ with a sensitivity correction factor higher than $\pm 5\%$ was excluded from the further experiment.

Calibration factor of nanoDot™

Upon calibrating the nanoDot™ dosimeter with an

ionization chamber, the nanoDot™ dosimeter's average radiation dose was 84.18 cGy, while the ionization chamber's average radiation dose was 103.00 cGy. Therefore, the calibration factor was 1.22.

Dose uniformity of virtual bolus in breast VMAT planning and validation with nanoDot™ measurement

The distribution of breast dose was uniform, with the coefficient of variation (%CV) among 9 points being less than 3% for both calculation and measurement, except for the measured dose at 15 mm and -600 HU, as shown in Table 1.

Table 1. The difference in measured radiation dose versus calculated radiation dose from an average of 9 locations.

Thickness of virtual bolus (mm)	CT number of bolus (HU)	Measured dose (cGy)		Calculated dose (cGy)		%Dose difference
		Mean $\pm$ SD	%CV	Mean $\pm$ SD	%CV	
No virtual bolus	-	211.69 $\pm$ 5.60	2.65	208.16 $\pm$ 1.96	0.94	-1.67
10	0	211.83 $\pm$ 3.14	1.48	207.86 $\pm$ 1.85	0.89	-1.87
	-100	210.84 $\pm$ 2.94	1.39	206.02 $\pm$ 2.52	1.22	-2.29
	-200	212.04 $\pm$ 3.19	1.50	205.48 $\pm$ 2.07	1.01	-3.09
	-300	211.07 $\pm$ 5.07	2.40	204.80 $\pm$ 4.26	2.08	-2.97
	-400	210.14 $\pm$ 5.54	2.64	204.56 $\pm$ 4.52	2.21	-2.66
	-500	209.76 $\pm$ 5.61	2.67	204.17 $\pm$ 3.96	1.94	-2.66
	-600	205.39 $\pm$ 5.21	2.54	199.57 $\pm$ 3.81	1.91	-2.83
	-700	208.96 $\pm$ 3.19	1.53	201.78 $\pm$ 2.45	1.21	-3.44
15	0	217.06 $\pm$ 2.92	1.35	212.02 $\pm$ 2.27	1.07	-2.32
	-100	216.06 $\pm$ 5.59	2.59	211.50 $\pm$ 3.23	1.53	-2.11
	-200	213.68 $\pm$ 4.65	2.18	207.33 $\pm$ 4.88	2.35	-2.97
	-300	211.19 $\pm$ 4.34	2.06	205.89 $\pm$ 4.71	2.29	-2.51
	-400	209.71 $\pm$ 4.40	2.10	205.34 $\pm$ 4.43	2.16	-2.08
	-500	210.20 $\pm$ 4.57	2.17	205.43 $\pm$ 3.34	1.63	-2.27
	-600	207.68 $\pm$ 7.23	3.48	203.08 $\pm$ 5.26	2.59	-2.21
	-700	206.20 $\pm$ 5.42	2.63	202.49 $\pm$ 4.93	2.43	-1.80

Note: %CV: $(SD/Mean) \times 100$, %dose difference: $\frac{(Calculated\ dose - Measured\ dose)}{Measured\ dose} \times 100$

By measuring the dose in the Rando phantom using the nanoDot™ dosimeter, which underwent corrections for sensitivity and calibration factors, it was determined that the discrepancy between the measured dose and the dose calculated from the treatment plan system averaged across nine locations in a treatment plan that excluded virtual bolus.

In treatment plans where a 10-mm virtual bolus at 0 HU to -700 HU was applied, the discrepancy ranged from 1.87% to -3.44%. Similarly, in treatment plans employing a 15-mm virtual bolus within the same HU range, the variation ranged from -1.80% to -2.97%, as shown in Table 1. Importantly, all treatment plans demonstrated dose differences of less than $\pm 5\%$, under the recommendations outlined in the IAEA Human Health Report No. 8. ²²

Application of virtual bolus in breast cancer patient plans

In the treatment plans involving adjustments of the thickness of the virtual bolus and modifications of the CT number of the virtual bolus, $D_{95\%}$ for all treatment plans were consistently found to be at least 95% of the prescribed dose or 47.5 Gy. Similarly, the D_{max} value for all treatment plans was maintained at not higher than 115% of the prescribed dose or 57.5 Gy. Notably, a reduction trend was observed with lower CT values in treatment plans featuring identical thicknesses of the virtual bolus, as illustrated in Table 2. The CN for all plans ranged between 0.78-0.85, and HI ranged between 0.08-0.15. The averages and the standard deviations among 10 breast cancer patients for all plans are shown in Table 2.

Table 2 The average dose of PTV in the treatment plan of 10 breast cancer patients.

Virtual bolus		Dose parameters		CN	HI
Thickness (mm)	CT number (HU)	D_{max} (Gy)	$D_{95\%}$ (Gy)		
No virtual bolus	-	55.61±0.82	50.01±0.01	0.83±0.04	0.08±0.01
10	0	56.18±0.51	50.08±0.09	0.80±0.06	0.10±0.01
	-100	57.23±1.22	49.10±0.98	0.82±0.06	0.13±0.04
	-200	56.89±0.99	48.85±0.95	0.83±0.05	0.13±0.04
	-300	56.60±1.24	48.74±0.97	0.83±0.05	0.12±0.04
	-400	56.49±1.25	48.51±1.09	0.83±0.05	0.13±0.04
	-500	56.17±0.99	48.41±1.04	0.84±0.06	0.13±0.04
	-600	56.27±0.95	48.21±0.92	0.85±0.05	0.13±0.04
	-700	56.32±1.22	47.99±1.40	0.84±0.07	0.13±0.05
15	0	56.36±0.63	50.23±0.25	0.78±0.06	0.11±0.01
	-100	57.31±1.31	48.97±1.06	0.79±0.05	0.15±0.05
	-200	56.93±1.40	48.80±0.98	0.80±0.05	0.15±0.05
	-300	56.52±1.21	48.63±0.99	0.81±0.05	0.14±0.05
	-400	56.22±1.46	48.36±0.97	0.82±0.05	0.14±0.04
	-500	56.12±1.65	48.00±1.01	0.83±0.05	0.14±0.05
	-600	55.49±1.39	47.84±1.05	0.84±0.04	0.14±0.05
	-700	55.55±1.69	47.73±0.96	0.84±0.04	0.14±0.04

Note: CN: conformity number, HI: homogeneity index, D_{max} : maximum dose, $D_{95\%}$: dose received by 95% of the target volume.

As illustrated in Table 3, the treatment plan without a virtual bolus received the lowest dose to organs at risk compared to the plans with a virtual bolus. In the virtual bolus plans, considering the absorbed dose to organs, the V_{5Gy} of the lung on the lesion side did not exceed the specified dose range of 55% of the lung volume in all treatment plans utilizing a virtual bolus with a thickness of 10 mm, except for those with a CT number of -600 HU.²¹ For the virtual bolus with a thickness of 15 mm, only the treatment plans with a CT number of 0 HU met the criteria.

Regarding the D_{mean} of the heart, limited to a radiation dose not exceeding 5 Gy, it was observed that only treatment plans utilizing virtual bolus with CT number of 0 HU for thicknesses of 10 and 15 mm met the specified criteria. For V_{10Gy} , restricted to not exceeding 35% of the heart volume, this criterion was met within the defined threshold across all treatment plans, as indicated in Table 3.

Considering the dose parameter for tumors and organs at risk, the optimal CT number for the virtual bolus was 0 HU for both 10 mm and 15 mm thicknesses.

Table 3. The average dose of the lungs and heart in the treatment plan of 10 breast cancer patients.

Virtual bolus		Lung		Heart	
Thickness (mm)	CT number (HU)	V_{5Gy} (%)	D_{mean} (Gy)	V_{10Gy} (%)	
No virtual bolus	-	43.43±4.33	4.10±0.62	7.80±1.88	
10	0	44.31±4.43	4.24±0.65	8.81±1.76	
	-100	53.21±8.67	5.35±1.47	12.30±6.43	
	-200	54.64±9.17	5.51±1.51	12.85±6.76	
	-300	53.32±8.80	5.49±1.39	12.72±6.54	
	-400	53.57±9.85	5.35±1.38	12.25±6.05	
	-500	54.10±10.03	5.40±1.42	12.22±6.06	
	-600	55.20±9.48	5.45±1.44	12.37±5.91	
	-700	54.63±11.19	5.39±1.50	12.28±6.55	
15	0	45.41±5.38	4.39±0.43	9.23±1.40	
	-100	59.49±10.16	6.06±1.09	14.09±4.70	
	-200	59.99±9.46	5.93±1.06	13.55±4.51	
	-300	59.27±8.46	5.93±1.19	13.69±5.29	
	-400	59.42±10.74	5.77±1.16	12.99±4.79	
	-500	61.19±10.39	5.88±1.24	13.42±5.25	
	-600	60.11±8.80	5.77±1.11	13.21±5.10	
	-700	59.40±9.51	5.78±1.19	13.05±4.89	

Note: V_{5Gy} : volume of an organ receiving a radiation dose of at least 5Gy, V_{10Gy} : volume of an organ receiving a radiation dose of at least 10Gy, D_{mean} : mean dose received by an organ at risk.

Discussion

From the dose measurement of the VMAT technique, nanoDot™ with corrected sensitivity and calibration factors was utilized. The results indicated that the difference between the measured dose and the dose calculated from the treatment planning system at an average of nine locations did not exceed ±5%, as recommended by the IAEA Human Health Report No. 8.²² However, the discrepancy between the measured dose and doses calculated from the treatment planning system might have been attributed to the volumetric intensity-modulated irradiation techniques with high dose gradients at the edge of the field. At specific points, there could have been a small field or radiation-measuring device at the edge of the beam. Moreover, the breast anatomy has a sloped surface, resulting in the placement of the device not being planar at the same level. In the event of measurement, it should have been studied in conjunction with other small dosimeters, such as metal oxide semiconductor field-effect transistor (MOS-FET) dosimeter, radiophotoluminescence glass dosimeter (RPLGD). Additionally, locations where the difference exceeded 5% could have been attributed to the angular independence of this device. A previous study by Kern JR *et al.* reported the nanoDot™ exhibited a significant angular sensitivity when exposed to photon beams.²³ The angular dependence was 4% lower at 6 MV and 3% lower at 18 MV compared to the response observed when exposed to nominal incident beams.

Considering breast movement, a study by Frazier RC *et al.* found that inhalation moved the breasts forward,

with an average movement of 6 mm (range: 3-11 mm) and 4 mm (range: 1-7 mm) at the inner and lateral edges, respectively.²⁴ The virtual bolus thickness in this study, 10 and 15 mm, covered the range of breast movement.

Based on the study of the application of virtual bolus in treatment plans, adjustments were made to the thickness of the virtual bolus, and changes were made to the CT number of bolus. This study reduced CT numbers of bolus to evaluate radiation doses from treatment plans. The treatment plan met all criteria utilizing virtual bolus with 10- and 15-mm thicknesses, with CT number values set to 0 HU. Furthermore, virtual bolus materials did not change the radiation dose in sensitive organs. This finding differs from a study by Lizondo M *et al.* which found that the most suitable CT numbers were approximately -400 HU and -550 HU for tissue equivalence materials with 10 mm and 15 mm thicknesses, respectively.¹ Therefore, the negative CT value was chosen in the current investigation. Discrepancies in the optimal CT number between this research and that conducted by Lizondo M *et al.* could be attributed to the influence of intra- and inter-fractional motion on position uncertainty, which was simulated through the utilization of the plan uncertainty feature integrated into Eclipse. Nevertheless, the actual motion of the breast during breathing cycles was not explored in this study. Future investigations could involve the evaluation of clinical cases to analyze virtual bolus VMAT plans or the utilization of a moving breast phantom to examine virtual bolus in the Flash region.

Conclusion

The difference between the measured dose and the dose calculated from the 9-position in breast falls within $\pm 5\%$, aligning with the recommendation from the IAEA Human Health Report No. 8. The most significant difference, 6.36% (observed at the third position with a 10 mm thickness and a CT number of -700 HU in the bolus plan), is noted. For clinical plans, it is concluded that treatment plans utilizing virtual bolus are effective in meeting all dose criteria. Specifically, the plans employing 10- and 15-mm thicknesses with CT numbers equal to 0 HU demonstrate favorable outcomes. Only treatment plans with a CT number of 0 HU for organs at risk meet the criteria.

Further investigations are warranted to evaluate the measurement of radiation dose in actual patients. This includes assessing the broader population subjected to treatment plans involving virtual bolus. A larger sample size would facilitate more comprehensive evaluations.

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References

- [1] Lizondo M, Latorre-Musoll A, Ribas M, Carrasco P, Espinosa N, Coral A et al. Pseudo skin flash on VMAT in breast radiotherapy: Optimization of virtual bolus thickness and HU values. *Physica Medica* 2019; 63: 56-62. doi: 10.1016/j.ejmp.2019.05.010.
- [2] Monajemi TT, Oliver PAK, Day A, Yewondwossen M. In search of a one plan solution for VMAT post-mastectomy chest wall irradiation. *J Appl Clin Med Phys* 2020; 21(8): 216-23. doi:10.1002/acm2.12948.
- [3] Bogue J, Wan J, Lavey RS, Parsai El. Dosimetric comparison of VMAT with integrated skin flash to 3D field-in-field tangents for left breast irradiation. *J Appl Clin Med Phys* 2019; 20(2): 24-9. doi:10.1002/acm2.12527.
- [4] ICRU. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT), ICRU Report 83. 2010. doi:10.1093/jicru/ndq010.
- [5] Rossi M, Boman E, Skyttä T, Haltamo M, Laaksomaa M, Kapanen M. Dosimetric effects of anatomical deformations and positioning errors in VMAT breast radiotherapy. *J Appl Clin Med Phys* 2018; 19(5): 506-16. doi:10.1002/acm2.12409.
- [6] Tyran M, Tallet A, Resbeut M, Ferre M, Favrel V, Fau P et al. Safety and benefit of using a virtual bolus during treatment planning for breast cancer treated with arc therapy. *J Appl Clin Med Phys* 2018; 19(5): 463-72. doi:10.1002/acm2.12398.
- [7] Yukihiro EG, Yoshimura EM, Lindstrom TD, Ahmad S, Taylor KK, Mardirossian G. High-precision dosimetry for radiotherapy using the optically stimulated luminescence technique and thin Al₂O₃:C dosimeters. *Phys Med Biol* 2005; 50(23): 5619-28. doi:10.1088/0031-9155/50/23/014.
- [8] Jursinic PA. Characterization of optically stimulated luminescent dosimeters, OSLDs, for clinical dosimetric measurements. *Med Phys* 2007; 34(12): 4594-604. doi:10.1118/1.2804555.
- [9] Dunn L, Lye J, Kenny J, Lehmann J, Williams I, Kron T. Commissioning of optically stimulated luminescence dosimeters for use in radiotherapy. *Radiat Meas* 2013; 51-2: 31-39. doi:10.1016/j.radmeas.2013.01.012.
- [10] Viamonte A, Da Rosa LAR, Buckley LA, Cherpak A, Cygler JE. Radiotherapy dosimetry using a commercial OSL system. *Med Phys* 2008; 35(4): 1261-6. doi:10.1118/1.2841940.
- [11] Alvarez P, Kry SF, Stingo F, Followill D. TLD and OSLD dosimetry systems for remote audits of radiotherapy external beam calibration. *Radiat Meas* 2017; 106: 412-5. doi:10.1016/j.radmeas.2017.01.005.
- [12] Mrčela I, Bokulić T, Izewska J, Budanec M, Fröbe A, Kusić Z. Optically stimulated luminescence in vivo dosimetry for radiotherapy: Physical characterization and clinical measurements in 60Co beams. *Phys Med Biol* 2011; 56(18): 6065-82. doi:10.1088/0031-9155/56/18/018.
- [13] Yusof FH, Ung NM, Wong JHD, Jong WL, Ath V, Phua VCE et al. On the use of optically stimulated luminescent dosimeter for surface dose measurement during radiotherapy. *PLoS One* 2015; 10(6): 1-15. doi: 10.1371/journal.pone.0128544.
- [14] Zhuang AH, Olch AJ. Validation of OSLD and a treatment planning system for surface dose determination in IMRT treatments. *Med Phys* 2014; 41(8): 081720doi:10.1118/1.4890795.
- [15] Wake JR, Chen FQ, Ashworth S, Byth K, Wang W, Stuart KE. Verification using in vivo optically stimulated luminescent dosimetry of the predicted skin surface dose in patients receiving postmastectomy radiotherapy. *Medical Dosimetry* 2021; 46(2): e1-e6. doi:10.1016/j.meddos.2020.10.001.
- [16] Butson M, Chen T, Alzaidi S, Pope D, Butson E, Gorjiara T et al. Extrapolated skin dose assessment with optically stimulated luminescent dosimeters. *Biomed Phys Eng Express* 2016; 2(4): 47001. doi:10.1088/2057-1976/2/4/047001.
- [17] Raj LJS, Pearlin B, Peace BST, Isiah R, Singh IRR. Characterisation and use of OSLD for in vivo dosimetry in head and neck intensity-modulated radiation therapy. *J Radiother Pract* 2021; 20(4): 448-54. doi:10.1017/S146039692000062X.
- [18] Ponmalar R, Manickam R, Ganesh KM, Saminathan S, Raman A, Godson HF. Dosimetric characterization of optically stimulated luminescence dosimeter with therapeutic photon beams for use in clinical radiotherapy measurements. *J Cancer Res Ther* 2017; 13(2): 304-12. doi:10.4103/0973-1482.199432.
- [19] IAEA. Absorbed Dose Determination in External Beam Radiotherapy, Technical Reports Series No. 398 (Rev. 1). INTERNATIONAL ATOMIC ENERGY AGENCY:

- Vienna, 2024; doi:10.61092/iaea.ve7q-y94k.
- [20] Feuvret L, Noël G, Mazeron JJ, Bey P. Conformity index: A review. *Int J Radiat Oncol Biol Phys* 2006; 64(2): 333-42. doi:10.1016/j.ijrobp.2005.09.028.
- [21] Freedman GM, White JR, Rosenstein B, Bentzen SM, Li A, Co-Chair S et al. Radiation therapy oncology group RTOG 1005 a phase III trial of accelerated whole breast irradiation with hypofractionation plus concurrent boost versus standard whole breast irradiation plus sequential boost for early-stage breast cancer, Study Chairs Document History. 2011 [cited 2024 May 14]. Available from: <https://www.ctsu.org>.
- [22] IAEA. Development of Procedures for In Vivo Dosimetry in Radiotherapy, IAEA HUMAN HEALTH REPORTS No. 8. 2013 [cited 2024 May 14]. Available from: https://www-pub.iaea.org/MTCD/publications/PDF/Pub1606_web.pdf.
- [23] Kerns JR, Kry SF, Sahoo N, Followill DS, Ibbott GS. Angular dependence of the nanoDot OSL dosimeter. *Med Phys* 2011; 38(7): 3955-62. doi:10.1118/1.3596533.
- [24] Frazier RC, Vicini FA, Sharpe MB, Yan D, Fayad J, Baglan KL et al. Impact of breathing motion on whole breast radiotherapy: A dosimetric analysis using active breathing control. *Int J Radiat Oncol Biol Phys* 2004; 58(4): 1041-7. doi:10.1016/j.ijrobp.2003.07.005.

Analysing the effectiveness of cognitive behavioural therapy in university students with ADHD: A systematic review

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ABSTRACT

Background: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood and often persists into adult life. University students with ADHD frequently experience great difficulty with global academic functioning, resulting in higher drop-out rates and, consequently, higher unemployment rates.

Objective: This literature review aims to analyse the effectiveness of cognitive behavioural therapy (CBT) interventions to reduce ADHD-related symptoms in university students with ADHD.

Materials and methods: A literature search was conducted via EBSCO database in October 2023 using key terms: ADHD OR attention deficit hyperactivity disorder AND cogniti* intervention OR cogniti* therapy AND college student* OR university student*. The inclusion criteria were studies using cognitive behavioural therapy as their primary intervention for individuals with ADHD who are enrolled in university or college and are 18 years or above in age.

Results: Seven out of 115 papers were deemed eligible and were included in this review. This review's studies included four randomized control trials and three before and after open trials. Three key themes were identified through data extraction: intervention design, outcome measures used, and effectiveness of interventions on ADHD-related symptoms. All the studies tailored their CBT intervention toward university students. There was a statistically significant improvement in core domains of ADHD-related impairment, in particular, inattention (N=7), overall executive functions (n=5), and hyperactivity-impulsivity (N=1).

Conclusion: While the current findings suggest positive results of CBT for reducing ADHD-related symptoms in university students with ADHD, further research should explore the sustainability of these gains over the long term. Due to the lack of explicit published study on this topic in the United Kingdom, further research should be conducted in the UK to assess the applicability and effectiveness of tailored CBT interventions within the British university environment.

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that begins in early childhood and often persists into adult life.¹ As stated in the Diagnostic and Statistical Manual-5 (DSM-5), ADHD is characterized by persistent inattention, hyperactivity, and impulsivity.² These symptoms will manifest in two or more settings, such as home and work.² A study conducted by Emmers *et al.* identified that university students with ADHD have more difficulty with global academic functioning compared to those without ADHD. These academic

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difficulties can be seen as poor academic performance in time-limited exams, lower social adjustments, social skills etc. impacting academic performance.³ Academic difficulties in turn may result in a higher risk of dropping out of university causing individuals with ADHD to have fewer years of education and higher unemployment rates compared to those who do not have ADHD.⁴ Along with academic difficulties, it has been reported across the board that students with ADHD have higher rates of comorbidities that include both internal and external symptom domains negatively impacting the mental wellbeing of students.⁵ Cognitive Behavioural Therapy (CBT) is a structured and time-limited approach which aims to reduce individuals' distress and promote adaptive cognitions and behaviours by exploring the links between thoughts, emotions and behaviours.⁵

A consensus statement from the United Kingdom (UK) Adult ADHD Network highlighted that within the UK's Higher Education Institutions (HEIs), ADHD is categorised as a Specific Learning Disability or Difference (SpLD) rather than a mental health condition. This categorisation as an SpLD makes ADHD a hidden disability in HEIs, contributing to the marginalization of affected students.³ Unfortunately, this classification hinders data collection on the prevalence of ADHD in UK HEIs. As a result, the only available prevalence data is for ADHD in adults, estimated at 3-4%.⁶

With an increasing number of ADHD diagnoses in the UK, understanding the efficacy of ADHD interventions is crucial for Occupational Therapists (OTs) seeking evidence-based practices. ADHD influences several dimensions of an individual's life, and OTs recognise that these impacts extend beyond the immediate domains, encompassing academic and social realms. University students with ADHD face unique academic and personal challenges that significantly impact their success. These students often struggle with time management, poor study skills, and difficulty focusing, which leads to procrastination and missed deadlines.⁷ These difficulties are exacerbated by the transition to independent living, as students must manage responsibilities formerly overseen by parents or teachers, such as organizing belongings and structuring their time.⁷ Consequently, students with ADHD tend to have lower Grade Point Averages (GPA), higher rates of academic probation, and are more likely to withdraw from courses or not graduate. Moreover, the heightened presence of immediate social rewards in college settings can further distract students from academic tasks, leading to increased engagement in activities like partying or social media use over studying, a phenomenon known as "temporal discounting".⁷ The presence of comorbid conditions such as anxiety, depression, or substance use disorders further complicates their academic and emotional regulation, posing additional challenges to their executive functioning.⁸

Occupational therapists have the potential to integrate CBT-informed strategies into their practice to address academic challenges, executive-functioning deficits and emotional well-being with this population. Additionally,

the Royal College of Occupational Therapists (RCOT) recently highlighted the important role OTs have within a university in supporting students' wellbeing.⁹ A consensus statement from the UK ADHD Network highlights areas for potential occupational therapy development. These areas include organisation of environments, enhancing social interactions and awareness, developing stress management techniques as well as monitoring and regulating sensory integration for students with ADHD.¹⁰

When a broad literature search was conducted, there appeared to be a shortfall in published research regarding the university-based and adult population compared to that found regarding ADHD interventions within school-based settings, paediatric and adolescent populations. This literature review therefore aims to bridge this gap by analysing the effectiveness of CBT interventions to reduce ADHD-related symptoms in university students with ADHD. The formulation of this review question adhered to the Population, Intervention, Comparison, Outcome (PICO) model¹¹ where the population included university students with ADHD, intervention being cognitive behavioural therapy and effect of the intervention on ADHD-related symptoms as the outcome ensuring a well-constructed and organised structure.

Methodology

A literature review is the comprehensive study and interpretation of literature that addresses a specific question with the aim of identifying and critiquing the existing literature on a specific topic.¹² Literature reviews support healthcare professionals in fulfilling their professional obligations by ensuring they stay informed about the latest developments and research that shape their practice.¹²

Search strategy

A systematic and rigorous approach was undertaken when designing and conducting the search for literature to ensure that all relevant literature was retrieved.¹²

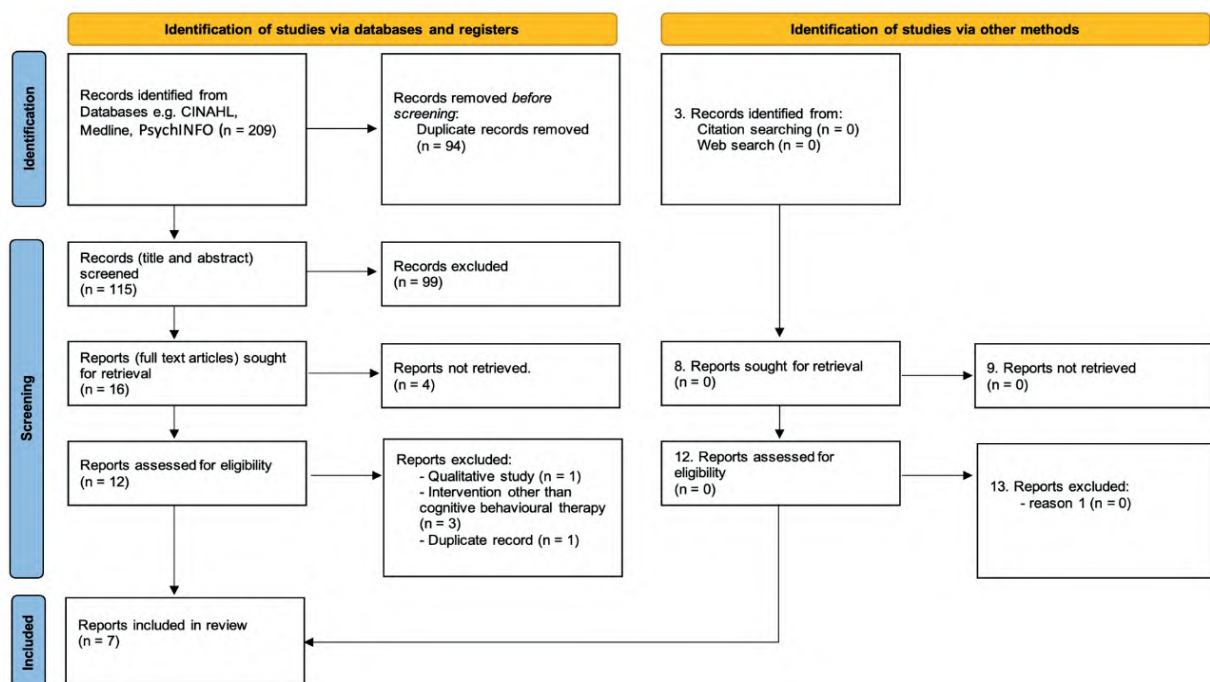
Guided by the terms characterised by the PICO model¹¹, relevant search terms were generated, ensuring to include relevant synonyms and spellings (Supplementary material Appendix A). These search terms were entered into EBSCO host database (including Academic Search Ultimate, APA PsycArticles, APA PsycBooks, APA PsycInfo, Art & Architecture Complete, Business Source Ultimate, Communication Source, eBook Collection (EBSCOhost), eBook Academic Collection (EBSCOhost), eBook Open Access (OA) Collection (EBSCOhost), Education Source, Environment Complete, ERIC, European Views of the Americas: 1493 to 1750, GreenFILE, Hospitality & Tourism Complete, Library, Information Science & Technology Abstracts, MEDLINE Complete, Regional Business News, SocINDEX with Full Text, SPORTDiscus with Full Text, CINAHL Ultimate) in October 2023, which identified 209 records. Whilst screening the titles and abstracts of the resulting records, the inclusion and exclusion criteria (Table 1) were applied to identify studies that are eligible to be included in the final literature review.

Table 1. Inclusion and exclusion criteria.

Inclusion	- Primary research that included interventions incorporating cognitive behavioural therapy (CBT) techniques, characterised by the adaption of cognition and behaviours designed to enhance coping mechanisms and reduce individual's distress. - Studies that are published in peer reviewed journals. - Studies involving adult participants (aged 18 years and older) with diagnosed ADHD, who were enrolled in college or university at the time of study. - Studies that utilise a minimum of one ADHD-related outcome measure specifically assessing core ADHD-related domains.
Exclusion	- Studies that are qualitative in nature. - Studies that are published in languages other than English language.

Participants with comorbidities such as substance abuse disorder, suicidality, psychotic disorder, bipolar disorder and autism spectrum disorder posed a significant challenge to establish the true relationship between the intervention and outcome in the extracted data. This was seen as a potential weakness of extracted data as it negatively influenced the outcomes with increased numbers of confounding variables. Despite this, samples with comorbidities were retained. This decision was driven by the belief that including such samples would enhance the generalisability of the findings ^{1,3}. Given that 75% of adults with ADHD also experience at least one other mental health disorder, often anxiety or mood

disorders, the inclusion of comorbidities ensured a more accurate representation of the overall population.¹⁴ Inclusion criteria affirmed that the study participants were enrolled in college or university with a confirmed diagnosis of ADHD which aided strict adherence to the target population. Given the prior description of CBT, Dialectical Behaviour Therapy (DBT) is within this category, allowing its inclusion in the literature review.¹⁵ As detailed in the PRISMA flow diagram¹⁶ (Figure 1), the inclusion and exclusion were applied and seven out of the original 115 records were deemed eligible and were included for this literature review.

**Figure 1.** PRISMA diagram (Page et al. 2021)

Critical appraisal

Critical appraisal involves the methodical evaluation of research evidence to assess its reliability, significance and applicability within a specific context.¹⁷ It is important to critically appraise the literature to ensure that the findings are interpreted considering the strengths and weaknesses apparent to the researcher's methodology.¹⁸

The selected articles (n=7) were all critically evaluated using The McMaster Critical Review Form for Quantitative Studies¹⁹ (Supplementary material, Appendix B and C) with an overview table is presented in (Supplementary material, Appendix D). Use of a standard critical appraisal tool ensured the consistency of quality appraisal process in an unbiased manner.²⁰ The 'McMaster Critical Review Form for Quantitative studies' proves to be an appropriate tool to use due to its comprehensive assessment of methodological quality of quantitative evidence as well as its accommodations to a wide range of research designs. This tool also contains a detailed guideline to assist reviewers maintain their consistency in evaluating methodological quality.²⁰

The before and after study design was adopted by three studies resulting in the researchers omitting the use of a control group.^{13,21,22} The absence of a control group precludes blind assessments of outcomes and does not account for confounding factors.²³ Whilst medication co-intervention was not avoided across the included studies and in attempt to reduce impacts on outcomes, and supported by Aggarwal and Ranganathan (2019), authors reported that the students were required to be on a stable dose of medication for a minimum of four weeks prior to and throughout the intervention program and to report any changes where applicable.^{7,8,15,22,24} All studies had a strength of detailing the participant characteristics, remaining focused on the aim and justifying their studies in relation to previous literature. This is seen as a strength as it is important to have clear direction and justifications.

Results and findings

A data extraction table summarises the final seven studies included in this literature review (Supplementary material Appendix D). Only two of the final seven studies were conducted outside of the United States of America, namely Solanto and Scheres (2021) in the Netherlands and Van der Oord et al. (2020) in Belgium. The study's publication date ranges from 2010 to 2023. All papers focused on identifying the effectiveness of their respective tailored or adapted cognitive interventions for university students with ADHD. Throughout the seven studies, all participants had a confirmed diagnosis of ADHD prior to commencing the intervention with a cumulative age range of 18- to 38-year-olds. The most common comorbidity among the participants across these studies was anxiety and depression. Three studies conducted randomized control trials^{8,15,24} whilst the remaining studies were conducted as open clinical trials, with a cumulative sample size range of 17-250 individuals. Overall, the included papers had moderate to strong quality appraised using the McMaster Critical Review tool.¹⁹

Type of intervention and design

The interventions were either specifically adapted from a previous adult ADHD programme or newly designed, to provide a tailored intervention for university students with ADHD as all the studies acknowledged that university students with ADHD experience different difficulties and have different priorities when compared to the remaining adult ADHD population.

The cumulative intervention timelines range from 6 to 12 weeks, with an average and modal length of 8 weeks, allowing the intervention to be run within the students' academic calendar. The interventions implemented in all the studies were designed to deliver weekly therapy sessions, with an average session duration of one hour. The sessions varied in format, encompassing group or individual formats. Majority of the interventions incorporated a blend of both group and individual sessions. Fleming *et al.* (2015), Van der Oord *et al.* (2020), Anastopoulos *et al.* (2021) and Anastopoulos and King (2015) invited participants to attend a booster session that took place in the following semester with the aim of maintaining the previously learnt skills.

All the interventions focused on aspects such as behavioural strategies and cognitive therapy, however Anastopoulos *et al.* (2021), Anastopoulos and King (2015), LaCount *et al.* (2015) and Hartung *et al.* (2022) had an additional focus on psychoeducation. Specific modules and topics addressed in each intervention are detailed in the data extraction table (Supplementary material Appendix D).

Outcome measures used

Within the seven final studies, 46 unique outcome measures were utilised. Among all the studies, assessments focusing on ADHD symptoms and ADHD-cognitive related impairments were used as the primary outcome measures. Majority of the studies included secondary outcome measures which assessed comorbidity symptoms such as depression and anxiety as well as assessed academic performance via participants' Grade Point Average (GPA). All studies employed one diagnostic measure at minimum for participant selection. The most commonly used primary outcome measure was the Conners Adult ADHD Rating Scale, Self-Report, Long Version²⁵ (CAARS-S:L) which was implemented by four studies^{7,8,13,21} and the most common secondary outcome measure was Becks Depression Inventory – 2nd edition⁸ (BDI-2) which was employed by five studies.^{7,8,13,15,24}

Effectiveness of interventions on ADHD-related symptoms

All studies reported an improvement in the ADHD-related cognitive domains/impairments assessed in their respective primary outcome measures. The core domains of impairment for ADHD which yielded statistically significant improvements are inattention^{7,8,13,15,22,24,26}, overall executive functions^{7,8,13,15,24}, overall ADHD symptomology^{8,13,26} and organisational, time management and planning skills.^{7,24,26} Anastopoulos *et al.* (2021) was the only study to report statistically significant improvement

in hyperactive-impulsive symptoms.

Other statistically significant findings included improvement in quality of life, mindfulness¹⁵ and memory⁷, as well as improvements in the school and work domain²² and self-concept domain²⁰ on the Weiss Functional Impairment Rating Scale²⁷ (WFIRS) and improvement on concentration and motivation on the Learning and Study Skills Inventory^{7,29} (LASSI-3rd edition).

Additionally, Anastopoulos *et al.* (2021) and Anastopoulos and King (2015) reported several statistically significant improvements including, improvement in ADHD knowledge on Test of ADHD Knowledge (TOAK), improvement in behavioural strategies and a decline in maladaptive thinking.

Van der Oord *et al.* (2020) reported statistically significant improvements in attitude, motivation and test strategies measured on LASSI however there was no differential impact in experimental group when compared to the control group.

Contrary to Fleming *et al.* (2015), Anastopoulos and King (2015) and Anastopoulos *et al.* (2021), who reported anxiety and depression symptoms to have no statistical significance, Van der Oord *et al.* (2020) and Solanto and Scheres (2021) reported a statistically significant improvement in depression and anxiety symptoms. However, there was no differential impact on experimental group when compared to control group in Van der Oord *et al.*'s (2020) study.

Four studies reported to have no statistically significant improvements on hyperactive-impulsive symptoms.^{48,21,22,24} Additionally, there was no reports of statistically significant improvements of GPA^{7,8,15}, self-concept and life skills domain on WFIRS²² and motivation on Barkley Deficits in Executive Function Scale^{7,29} (BDEFS).

Discussion

This literature review aims to identify the effectiveness of CBT interventions for reducing ADHD-related symptoms and deficits in university students with ADHD. Methodological analysis of the included studies revealed that number of studies reported a flaw regarding inadequate sample sizes to detect statistical power^{8,15,24}, adversely impacting the likelihood that a statistically significant finding actually reflects a true effect, furthermore, impacting generalisability.³⁰ There is a common threat to validity across the final studies. However, the findings from those studies may still be relevant as they do concur with findings reported in Hartung *et al.*'s (2022) study which has an adequate sample size to detect a medium effect. It is important to highlight the high prevalence of self-reported outcome measures across the final studies, acknowledging the potential for recall bias, however these outcome measures used are proven to be valid and reliable. As previously discussed, studies including comorbidities to their sample can be viewed in a negative light, however it may positively contribute to the generalisation of the findings as it mirrors the remaining ADHD population.⁸ Participant recruitment via self-referral was frequently viewed across the studies. This recruitment method may lead to selection bias as it inherently targets

high-functioning individuals with ADHD and those who are naturally motivated to instigate change and improvement, therefore potentially influencing results toward more favourable outcomes.

It must be highlighted that Anastopoulos and King (2015) and Hartung *et al.* (2022) had no reporting's on gaining informed consent, respective University Institutional Review Board approval or a description of ADHD diagnosis presentation, unlike the remaining studies.

This review focusses on discussion around three main themes such as location of the studies, the delivery format and the hyperactivity and inattention symptoms.

Location of the studies:

As previously identified and within the realm of this literature review's search strategy, no studies conducted in the UK were discovered. This is surprising as NICE (2019) guidelines for managing ADHD recommends CBT should be considered if the symptoms persist despite the use of medication. The lack of research published in the UK appears to be a common reporting across the board of research for ADHD in adults as Sedgwick (2018) too reported a paucity of research in the UK and Ireland in their literature review regarding the impact ADHD has on educational outcomes of university students. This lack of research could be due to the categorisation of ADHD as a disability in the UK and the HEIs providing reasonable adjustments for academic support, such as extended writing times or short rest breaks during exams, rather than providing interventions such as CBT.²⁹ Conducting additional research to explore the impact of reasonable adjustments and Cognitive Behavioural Therapy (CBT) interventions on university students with ADHD in the UK is recommended. The existing studies imply that CBT holds potential for enhancing academic performance and reduce ADHD-related deficits among students with ADHD.

Delivery format

Whilst traditional CBT interventions often include either group or individual therapy sessions, several studies have incorporated both group and individual sessions into their intervention. Individual sessions have advantages such as allowing the therapist to tailor their approach to the student and have a sole attention on that student whilst group therapy allows an opportunity for peer support, encouragement and a model of positive behavioural change.²¹ University students with ADHD have reported lower levels of social adjustment, social skills and self-esteem compared their non-ADHD peers.³¹ It is beneficial to incorporate group sessions as they are proven to foster a sense of belonging and reduce stigma both of which students with ADHD report have a negative impact on their wellbeing.^{32,22} The most prevalent delivery format among the included articles is that of group sessions used to address the content and the individual sessions used for mentoring, application and maintenance of the skills learnt in the group session. Several studies included booster sessions in their interventions^{8,13,15,24},

with Anastopoulos *et al.* (2021) highlighting the clinical benefits of members reconnecting and gaining additional peer support. Due the nature of the research studies, the lack of follow-up data and the similarity of findings, one cannot confidently conclude whether the delivery format impacts the effectiveness of the interventions on university students with ADHD. However, with the current level of knowledge and the acknowledged benefits, it is plausible to propose that integrating a combination of both group and individual sessions may have a greater impact on social domains of students. Consequently, this may lead to a reduction in ADHD-related symptoms, aligning with the aim of my literature review.

Hyperactive-impulsive and attention symptoms

The literature consistently highlights improvements in ADHD-related symptoms, with a focus on inattention and overall executive functioning across multiple studies. Interestingly, Anastopoulos *et al.* (2021) reported a unique statistically significant improvement in hyperactivity-impulsivity ($p=0.002$). Discrepancies in findings across studies may be attributed to factors such as the diminishing prevalence of hyperactivity-impulsivity with age, as emphasized by Willcutt's (2012) meta-analysis. Anastopoulos *et al.*'s (2021) larger participant pool of 250 participants and the predominance of ADHD-combined type (58.4%) contribute to the observed improvement in hyperactive-impulsive symptoms, unlike other studies with smaller samples with predominantly inattentive types.^{7,15,23,24} This indicates that the interventions included within this literature review are particularly effective in mitigating the inattention symptom and enhancing overall executive functions. The suggestion for future research is to adopt larger sample sizes and include more participants with combined or hyperactive-impulsive subtypes to assess intervention effectiveness within these specific diagnostic subtype populations. This suggestion aligns with the overarching aim of analysing the effectiveness of CBT interventions in reducing ADHD-related symptoms among university students with ADHD.

Conclusion

In conclusion, the heightened vulnerability of university students with ADHD to academic and psychosocial challenges necessitates effective interventions. Cognitive-behavioural therapy (CBT), as evidenced in the reviewed studies, shows promise in reducing ADHD-related symptoms, particularly inattention and executive dysfunction. While immediate positive outcomes are apparent, future research should explore the sustainability of these gains over the long term. Moreover, it is recommended that further studies be conducted in the UK to assess the applicability and effectiveness of tailored CBT interventions within the British university environment. Investigating the implementation of CBT by occupational therapists in an occupation-focused context presents an intriguing avenue for further exploration. Such investigations are crucial for enhancing the support systems available to students with ADHD, addressing both immediate and enduring needs.

Conflict of interest

None

References

- [1] Centers for Disease Control and Prevention (CDC). Attention-Deficit/Hyperactivity Disorder (ADHD) [online]. 2023. Available from: <https://www.cdc.gov/ncbddd/adhd/facts.html#print> [Accessed 23 November 2023].
- [2] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
- [3] Sedgwick-Müller JA, Müller-Sedgwick U, Adamou M, Catani M, Champ R, Gudjonsson G, Hank D, Pitts M, Young S, Asherson P. University students with attention deficit hyperactivity disorder (ADHD): a consensus statement from the UK Adult ADHD Network (UKAAN). *BMC Psychiatry*. 2022; 22:292. doi: 10.1186/s12888-022-04231-4
- [4] DuPaul GJ, Franklin MK, Pollack BL, Stack KS, Jaffe AR, Gormley MJ, Anastopoulos AD, Weyandt LL. Predictors and trajectories of educational functioning in college students with and without attention-deficit/hyperactivity disorder. *J Postsecond Educ Disabil*. 2018;31(2):161–78. doi: 10.1352/2326-6988-31.2.161
- [5] Fenn K, Byrne M. The key principles of cognitive behavioural therapy. *InnovAiT*. 2013;6(9):579-585. doi: 10.1177/1757177413506143
- [6] National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: How common is it? [Internet]. London: NICE; 2023. Available from: <https://cks.nice.org.uk/topics/attention-deficit-hyperactivity-disorder/background-information/prevalence/>. [Accessed 15 November 2023].
- [7] Solanto MV, Scheres A. Feasibility, acceptability, and effectiveness of a new cognitive-behavioral intervention for college students with ADHD. *J Atten Disord*. 2021;25(14):2068–2082. doi: 10.1177/1087054720979704
- [8] Anastopoulos AD, Langberg JM, Eddy LD, Silvia PJ, Labban JD. A randomized controlled trial examining CBT for college students with ADHD. *J Consult Clin Psychol*. 2021 Jan;89(1):21. doi: 10.1037/ccp0000545
- [9] Holding J. The role of occupational therapy in universities. *OT News*. December 2023:28-31.
- [10] Adamou M, Asherson P, Arif M, Buckenham L, Cubbin S, Dancza K, *et al.* Recommendations for occupational therapy interventions for adults with ADHD: a consensus statement from the UK adult ADHD network. *BMC Psychiatry*. 2021;21(72). doi:10.1186/s12888-021-03148-9.
- [11] Richardson WS, Wilson MC, Nishikawa J, Hayward RS. A well-built clinical question: A key to evidence-based decisions. *ACP J Club*. 1995;123
- [12] Aveyard H. *Doing a Literature Review in Health and Social Care: A Practical Guide*. Maidenhead: Open University Press; 2023.

- [13] Anastopoulos AD, King KA. A cognitive-behavior therapy and mentoring program for college students with ADHD. *Cogn Behav Pract.* 2015 May 1;22(2):141-51. doi: 10.1016/j.cbpra.2014.06.003
- [14] BMJ Best Practice. Attention deficit hyperactivity disorder in adults [online]. London: BMJ Publishing Group; 2023. Available from: <https://bestpractice.bmj.com/topics/en-gb/814> [Accessed 15 November 2023].
- [15] Fleming AP, McMahon RJ, Moran LR, Peterson AP, Driessens A. Pilot randomized controlled trial of dialectical behavior therapy group skills training for ADHD among college students. *J Atten Disord.* 2015;19(3):260-271. doi: 10.1177/1087054713507117
- [16] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Sue E Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021;321:160. DOI: 10.1136/bmj.n70
- [17] Mhaskar R, Emmanuel P, Mishra S, Patel S, Naik E, Kumar A. Critical appraisal skills are essential to informed decision-making. *Indian J Sex Transm Dis AIDS.* 2009;30(2):112–119. doi: 10.4103/0253-7184.59002
- [18] Tod D, Booth A, Smith B. Critical appraisal. *Int Rev Sport Exerc Psychol.* 2022;15(1):52-72. doi: 10.1080/1750984X.2021.1950144
- [19] Law M, Stewart D, Pollock N, Letts L, Bosch J, Westmorland M. Critical Review Form-Quantitative Studies. Ontario: McMaster University; 1998.
- [20] Hewitt-Taylor J. *The Essential Guide to Doing a Health and Social Care Literature Review.* Oxon: Routledge; 2017.
- [21] Hartung CM, Canu WH, Serrano JW, Vasko JM, Stevens AE, Abu-Ramadan TM, Bodalski EA, Neger EN, Bridges RM, Gleason LL, Anzalone C, Flory K. A new organizational and study skills intervention for college students with ADHD. *Cogn Behav Pract.* 2022;29(2):411–424. doi: 10.1016/j.cbpra.2020.10.004
- [22] LaCount PA, Hartung CM, Shelton CR, Clapp JD, Clapp TK. Preliminary evaluation of a combined group and individual treatment for college students with attention-deficit/hyperactivity disorder. *Cogn Behav Pract.* 2015;22(2):152-160. doi: 10.1016/j.cbpra.2014.09.003
- [23] Joy JE, Penhoet EE, Petitti DB. *Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis.* Washington: National Academies Press; 2005. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK22315/>. [Accessed 17 December 2023].
- [24] Van der Oord S, Boyer BE, Van Dyck L, Mackay KJ, De Meyer H, Baeyens D. A randomized controlled study of a cognitive behavioral planning intervention for college students with ADHD: An effectiveness study in student counseling services in Flanders. *J Atten Disord.* 2020;24(6):849–862. doi: 10.1177/1087054718757711
- [25] Conners CK, Erhardt D, Epstein JN, Parker JD, Sitarenios G, Sparrow E. Self-ratings of ADHD symptoms in adults I: Factor structure and normative data. *J Atten Disord.* 1999 Oct;3(3):141-51. doi: 10.1177/108705479900300303
- [26] Beck AT, Steer RA, Brown GK. *BDI-II, Beck depression inventory: Manual.* San Antonio, TX: Psychological Corp.; 1996.
- [27] Weiss MD. Weiss Functional Impairment Rating Scale (WFIRS) Self-Report [online]. Vancouver: University of British Columbia; 2000.
- [28] Weinstein CE, Palmer DR, Acee TW. *Learning and study strategies inventory (LASSI): User's manual.* 3rd ed. H&H Publishing Company, Inc.; 2016.
- [29] Barkley RA. *Barkley deficits in executive functioning scale (BDEFS).* New York: Guilford Press; 2011.
- [30] Dumas-Mallet E, Button KS, Boraud T, Gonon F, Munafò MR. Low statistical power in biomedical science: a review of three human research domains. *R Soc Open Sci.* 2017 Feb 1;4(2):160254. doi: 10.1098/rsos.160254
- [31] Shaw-Zirt B, Popali-Lehane L, Chaplin W, Bergman A. Adjustment, social skills and self-esteem in college students with symptoms of ADHD. *J Atten Disord.* 2005;8:109–120. doi: 10.1177/1087054705280140
- [32] Chew BL, Jensen SA, Rosén LA. College students' attitudes toward their ADHD peers. *J Atten Disord.* 2009 Nov;13(3):271-6. doi: 10.1177/1087054708325185
- [33] Hammell KW. Dimensions of meaning in the occupations of daily life. *Can J Occup Ther.* 2004;71:296-305. doi: 10.1177/000841740407100507
- [34] Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics.* 2012;9(3):490–499. doi: 10.1007/s13311-012-0135-8
- [35] Sedgwick JA. University students with attention deficit hyperactivity disorder (ADHD): a literature review. *Ir J Psychol Med.* 2018;35(3):221-235. doi: 10.1017/ipm.2018.19
- [36] Law M, MacDermid J. *Evidence-based rehabilitation.* 2nd ed. New Jersey: Slack; 1998.
- [37] National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management. London: NICE; 2019. NICE guidelines NG87.
- [38] Emmers E, Janssen D, Petry K, Van der Oord S, Baeyens D. Functioning and participation of students with ADHD in higher education according to the ICF-framework. *J Fur Higher Educ.* 2017;41:435-447.
- [39] Attention deficit hyperactivity disorder in adults - Symptoms, diagnosis and treatment. *BMJ Best Practice* [Internet]. Available from: <https://bestpractice.bmj.com/topics/en-gb/814>.
- [40] Aggarwal R, Ranganathan P. Study designs: Part 5—interventional studies (II). *Perspect Clin Res.* 2019 Oct 1;10(4):183-6. doi: 10.4103/picr.PICR_272_19

Supplementary Material:
Appendix A: Search Strategy

Research topic: The effectiveness of cognitive behavioural therapy interventions to reduce ADHD-related symptoms for university students with ADHD.	
	List other related words or terms
Search term 1: Attention deficit-hyperactivity disorder	ADHD or attention deficit hyperactivity disorder or attention deficit-hyperactivity disorder or ADD or attention deficit or attention deficit disorder
Search term 2: Cognitive intervention	Cogniti* intervention or cogniti* therapy or cogniti* treatment or cogniti* strategy or cogniti* program* or cogniti* practic* or cogniti* train*
Search term 3: University students	College student* or university student*
Results: 209 articles	
Peer reviewed: Yes	Publication date range: Published before October 2023
Age range: 18 years old and above	Languages: English
Research question: How effective is cognitive behavioural therapy interventions in reducing ADHD-related symptoms or deficits for university students with ADHD.	

Appendix B: Blank McMaster Critical Review Form**Blank McMaster Critical Review Form – Quantitative Studies (Law *et al.* 1998)****Article Title:****Reference:****URL:**

CITATION	Provide the full citation for this article in APA format:
STUDY PURPOSE Was the purpose stated clearly? ☐ Yes ☐ No	Outline the purpose of the study. How does the study apply to your research question?
LITERATURE Was relevant background literature reviewed? ☐ Yes ☐ No	Describe the justification of the need for this study:
DESIGN ☐ Randomized (RCT) ☐ cohort ☐ single case design ☐ before and after ☐ case-control ☐ cross-sectional ☐ case study	Describe the study design. Was the design appropriate for the study question? (e.g., for knowledge level about this issue, outcomes, ethical issues, etc.): Specify any biases that may have been operating and the direction of their influence on the results:
SAMPLE N = Was the sample described in detail? ☐ Yes ☐ No Was sample size justified? ☐ Yes ☐ No ☐ N/A	Sampling (who; characteristics; how many; how was sampling done?) If more than one group, was there similarity between the groups?: Describe ethics procedures. Was informed consent obtained?:
OUTCOMES Were the outcome measures reliable? ☐ Yes ☐ No ☐ Not addressed Were the outcome measures valid? ☐ Yes ☐ No ☐ Not addressed Outcome areas:	Specify the frequency of outcome measurement (i.e., pre, post, follow-up):
	List measures used:
INTERVENTION Intervention was described in detail? ☐ Yes ☐ No ☐ Not addressed Contamination was avoided? ☐ Yes ☐ No ☐ Not addressed ☐ N/A Cointervention was avoided? ☐ Yes ☐ No ☐ Not addressed ☐ N/A	Provide a short description of the intervention (focus, who delivered it, how often, setting). Could the intervention be replicated in practice?

RESULTS Results were reported in terms of statistical significance? ☐ Yes ☐ No ☐ N/A ☐ Not addressed Were the analysis method(s) appropriate? ☐ Yes ☐ No ☐ Not addressed	What were the results? Were they statistically significant (i.e., $p < 0.05$)? If not statistically significant, was study big enough to show an important difference if it should occur? If there were multiple outcomes, was that taken into account for the statistical analysis?
Clinical importance was reported? ☐ Yes ☐ No ☐ Not addressed	What was the clinical importance of the results? Were differences between groups clinically meaningful? (if applicable)
Drop-outs were reported? ☐ Yes ☐ No	Did any participants drop out from the study? Why? (Were reasons given and were drop-outs handled appropriately?)
CONCLUSIONS AND IMPLICATIONS Conclusions were appropriate given study methods and results ☐ Yes ☐ No	What did the study conclude? What are the implications of these results for practice? What were the main limitations or biases in the study?

Appendix C: Overview of McMaster Critical Review Results

Overview of McMaster Critical Review results (Law et al. 1998)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Fleming <i>et al.</i> , 2015	Y	Y	Y	Y	N	Y	Y	Y	NS	N	Y	Y	Y	Y	Y
Van der Oord <i>et al.</i> , 2020	Y	Y	Y	Y	Y	Y	Y	Y	NS	N	Y	Y	Y	Y	Y
Anastopoulos <i>et al.</i> , 2021	Y	Y	Y	Y	Y	Y	Y	Y	NS	N	Y	Y	Y	Y	Y
La Count <i>et al.</i> , 2015	Y	Y	Y	Y	Y	Y	Y	Y	NS	N	Y	Y	N	Y	Y
Anastopoulos and King, 2015	Y	Y	Y	Y	N	Y	Y	Y	NS	NS	Y	Y	N	Y	Y
Solanto and Scheres, 2021	Y	Y	Y	Y	N	Y	Y	Y	NS	N	Y	Y	Y	Y	Y
Hartung <i>et al.</i> , 2022	Y	Y	Y	Y	N	Y	Y	Y	NS	NS	Y	Y	Y	N	Y

Note: Q1: was the purpose stated clearly?, Q2: was relevant background literature reviewed?, Q3: was the design appropriate for the study question?, Q4: was the sample described in detail?, Q5: was sample size justified?, Q6: were the outcome measures reliable?, Q7: were the outcome measures valid?, Q8: was the intervention described in detail?, Q9: was contamination avoided?, Q10: was cointervention avoided?, Q11: were results reported in terms of statistical significance?, Q12: were the analysis methods appropriate?, Q13: was clinical importance reported?, Q14: were drop-outs reported?, Q15: were conclusions appropriate given study methods and results?, Y: yes, N: no, NS: not Specified.

Appendix D: Data Extraction Table

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Fleming <i>et al.</i> (2015), USA	Evaluating dialectical behaviour therapy (DBT) group skills training adapted for college students with Attention Deficit-Hyperactivity Disorder (ADHD)	Pilot Randomised Control Trial (RCT) The study was approved by the University of Washington Institutional Review Board.	33 students 18-24 years old 17 participants in DBT group (1 drop out) 16 participants in self-guided skills handout (SH) group Students were still eligible if they were on stable medication and dose for 1 month prior to enrolment. Intent-to-treat sample	DBT group skills training format 8 weeks - 8 weekly 90-minute group sessions focused on skills acquisition and strengthening - 7 weekly 10/15-minute individual coaching call focused on skills generalisation Booster - 90 min group session - First week follow up Setting - On campus outpatient psychology clinic Skills handout (SH) group (comparison group): - 34 pages of skills handouts and self-help materials drawn from a manual for treatment of adults with ADHD	- Barkley Adult ADHD Rating Scale – IV (BAARS-IV) - Brown ADD Rating Scale (BADS) - ADHD quality of life questionnaire (AAQoL) - Beck Anxiety Inventory (BAI) - Beck Depression inventory (BDI) - Grade Point Average (GPA) - Five facet Mindfulness Questionnaire (FFMQ) - Conners Continuous Performance Test – 2 nd edition (CPT-2)	Statistically significant: - Improvement in ADHD inattentive symptoms of DBT group compared to SH group at follow-up ($p=0.02$) - Improvement in executive functioning in DBT group compared to SH group ($p=0.007$) on BADDS total scores. - Improvement in quality of life of DBT group at post-treatment compared to SH group ($p=0.038$) - Improvement in overall mindfulness in DBT group at post-treatment and follow-up on FFMQ Not statistically significant: - No significant change in anxiety symptoms, depressive symptoms or GPA of DBT group compared to SH group. - A trend towards greater improvement in CPT-2 omission errors in DBT group compared to SH group ($p=0.066$). - No significant improvement of CPT-2 commission errors ($p=0.247$) or response time ($p=0.243$) in DBT group when compared to SH group. The authors report that the sample size does not provide enough statistical power to detect small-to-moderate effect sizes or to assess mediators and moderators of treatment response.

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Solanto and Scheres (2021), Netherlands	To assess the feasibility, acceptability, and effectiveness of a new group cognitive-behavioural treatment (CBT) to enhance executive function (EF) in college students with ADHD.	Pilot RCT The study was approved by the Institutional Review Board at the University where it was conducted. Reported all participants provided signed informed consent	ADHD group: 18 students 19-31 y/o (23.61 y/o) 56% female Typical comparison group: - 20 students - 18-22 y/o (19.85 y/o) - 95% female - Recruited from first-year psychology students Students who were taking medication for ADHD must be stable for 2 months.	Intervention aimed to impart both cognitive and behavioural strategies to facilitate development of the executive self-management skills in such a way that they would become habitual. 12 weeks - 12 weekly 2 hour group sessions - Weekly home exercises	Diagnostic assessments: - Conners Adult ADHD Rating Scale (CAARS-S) - Adult ADHD Self-report Scale (ASRS) - Conners adult ADHD rating scale - Adult ADHD Clinical Diagnostic Scale (ACDS) - Childhood ADHD Symptoms Scale (CSS) - Self-Report - DSM-5 - MINI International Neuropsychiatric Interview - AUDIT (alcohol) questionnaire - DUDIT (drugs) questionnaire Clinical outcomes: - Adult Investigator Symptoms Rating Scale (AISRS) - CAARS-Self-DSM Inattentive Symptoms sub- scale - CAARS-Self-Inattention/ Memory subscale - Beck Depression Inventory (BDI) - State-Trait Anxiety Inventory (STAI) - Penn state worry questionnaire Executive function outcomes: - Barkley Deficits in Executive Function Scale (BDEFS) - Learning And Study Skills Inventory (LASSI -3 rd edition) Educational outcome: - Grade point average (GPA) Participant evaluations: - Participants evaluation rating scale	Statistically significant: - Reduction in number of DSM-5 inattentive symptoms on clinician-rated AISRS ($p=0.001$) - Reduction of total score on AISRS ($p=0.000$) - Improvement for CAARS DSM-inattentive symptoms ($p=0.000$) - Decrease in CAARS-Self-Inattention/Memory subscale ($p=0.001$) - Reduction of self-management on BDEFS ($p=0.000$) - Improvements in organisation and total executive function - Improvement of motivation on LASSI ($p=0.012$) - Improvement of time-management on LASSI ($p=0.008$) - Improvement of concentration on LASSI ($p=0.002$) - Improvement of anxiety on LASSI ($p=0.005$) - Reduction of anxiety and depression symptoms on the Penn State Worry Questionnaire ($p=0.018$) Not statistically significant: - Improvement of motivation on BDEFS - Changes in GPA

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Van der Oord <i>et al.</i> (2020), Belgium	The effectiveness of a short individual cognitive behavioural planning intervention for college students with attention-deficit/hyperactivity disorder (ADHD)	RCT Reported clinical trial registration link. Reported all participants provided informed written consent.	59 students (1 excluded) 18 F; 41 M	Planning and organisation intervention adapted from the Dutch manual for adolescents with ADHD "Plan my Life" 6 week program - 6 weekly 1 hour individual sessions focused on enhancing planning and organisation of daily academic life Booster - 4 months after intervention focused on creating a relapse prevention plan Setting - College psychological services - At one site, individuals paid €15 per session	Selection measures: - Diagnostic Interview for Adult ADHD 2nd edition (DIVA 2.0) - MINI Plus - MSI-BPD - Structured clinical interview for DSM-IV Axis II personality disorders (SCID-II) Primary outcomes: - ADHD Rating Scale (ADHD-RS) - Learning And Study Skills Inventory (LASSI) Secondary outcomes: - Beck Depression Inventory II (BDI-II) - Delis-Kaplan Executive Function System (D-KEFS) - The Adult Self-Report (ASR)	Significant: - Reduction of inattention symptoms in ADHD group on ADHD rating scale - Overall change in ADHD symptoms over time on ADHD rating scale Both groups showed significant improvements in the following outcome measures, however there was no differential impact between the intervention group and wait list group: - Improvement in attitude, motivation, time management and test strategies on LASSI - Improvement of depressive symptoms on BDI - Improvement of executive functions on Tower Test - Improvement on attention problem subscale of the ASR Not statistically significant: - Reduction of hyperactivity symptoms on ADHD Rating Scale ($p=0.695$) Authors did not report data for the follow-up

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Anastopoulos <i>et al.</i> (2021), USA	Reports findings from a large, multisite randomized controlled trial examining the efficacy of a treatment for this population, known as ACCESS—Accessing Campus Connections and Empowering Student Success	RCT Multisite All study procedures were approved annually by each university's Institutional Review Board. Reported participants provided consent.	250 students 165 F; 85 M 18-30 y/o (19.7 y/o)	ACCESS CBT program Intensive active phase (8 weeks) - 8 weekly 90 minute group sessions focused on improving ADHD knowledge, behavioural strategies and adaptive thinking - 8 weekly 30 minute individual mentoring session focused on reinforcing what was learnt in CBT group, support student in establishing personal goals and signposting to appropriate resources Maintenance phase - One 90 minute booster group session at the start of the following semester - 6 flexible 30 minute individual mentoring sessions	Diagnostic measures: - Semi-Structured Interview for Adult ADHD - ADHD Rating Scale-5 (ARS-5) - Structured clinical interview for DSM-IV: Research Version (SCID-5-RV) Primary outcome measures: - Conners Adult ADHD Rating Scale, Self-Report, Long Version (CAARS-S:L) - Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A) - Beck Depression Inventory II (BDI-II) - Beck Anxiety Inventory (BAI) Secondary outcome measures: - Test of ADHD Knowledge (TOAK) - Strategies For Success (SFS) - ADHD Cognition Scale—College Version (ACS-CV) - Services for College Students Questionnaires (SCSQ)	Statistically significant: - Decline in overall ADHD symptomatology on CAARS Total ADHD scores ($p<0.001$) in both groups but greater in the ACCESS participants - Decline in inattention symptoms on CAARS IN scores ($p<0.001$) in both groups but greater in the ACCESS participants - Decline in hyperactive-impulsive symptoms on CAARS HI scores ($p=0.002$) in both groups but greater in the ACCESS participants. - Decline in overall EF deficits on BRIEF-A GEC scores ($p<0.001$) in both groups but significantly greater in the ACCESS participants. - Decline in behavioural regulation deficits on BRIEF-A BRI scores ($p<0.001$) - Decline in metacognition deficits on BRIEF-A MCI scores ($p<0.001$) in both groups but significantly greater in the ACCESS participants.

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
LaCount <i>et al.</i> (2015), USA	To investigate the preliminary effects of a CBT intervention, designed for adults with ADHD adapted to a combined group and individual format for college students with ADHD.	Open trial – before and after (no control group)	17 students (12 students completed post intervention)	Condensed adaptation a treatment protocol as a goal-directed intervention designed to help adults cope with ADHD.	- Barkley Current Symptom Scale – Self-Report Form (CSS-SR) - Weiss Functional Impairment Rating Scale (WFIRS)	- Improvement in ADHD knowledge on TOAK ($p<0.001$) in both groups but significantly greater in the ACCESS participants. - Improvement in use of behavioural strategies on SFS scores ($p<0.001$) in both groups but significantly greater in the ACCESS participants. - Decline in maladaptive thinking on ACS-CV ($p<0.001$) - Increase use of disability services ($p=0.001$) of ACCESS participants. Not statistically significant: - Reduction of depression symptoms on BDI-II ($p=2.97$) in both groups - Overall increase of ADHD medication ($p=0.513$) ADHD symptoms, EF and changes in clinical mechanisms were evident at the end of the active phase and remained stable throughout the maintenance phase of the intervention.
		The study was approved by the University Institutional Review Board where the study was conducted. Reported all participants provided informed consent.	18-38 y/o (25.41 y/o) 11 Female 6 Male Students were still eligible if they were on a stable course of medication.	10 weeks - 10 weekly 1 hour group sessions - 10 weekly 1 hour individual sessions Main modules: Psychoeducation, Organisation, and Planning; Reducing Distractibility; Adaptive Thinking and Additional Skills.		

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Anastopoulos and King (2015), USA	To identify the effectiveness of the ACCESS program for college students with ADHD.	Open trial -before and after study Foundation-funded project awarded to the University of North Carolina system. Participants providing informed consent was not reported.	43 students (3 drop-outs) 27 F; 16 M 17-27 y/o (20.3 y/o)	ACCESS CBT program Active treatment phase - 8 weekly 90 minute group CBT sessions - 8 weekly 30 minute individual mentoring sessions Maintenance phase - 2 booster CBT sessions at the start and midpoint of the semester - 5-6 30 min individual mentoring (occurring every 2-3 weeks) Main modules: ADHD knowledge, behavioural strategies, cognitive therapy	Clinical change mechanism: - 50-item test of ADHD Knowledge - Strategies For Success (SFS) - ADHD Cognitions Test (ACT) - Cognitive Response Test for ADHD (CRT-A) Functional Outcomes: - Conners Adult ADHD Rating Scale (CAARS-S:L) DSM-IV inattentive symptoms, DSM-IV hyperactive-impulsive symptoms, and DSM-IV ADHD symptoms total scores - Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) - Beck Depression Inventory -II (BDI-II) - Beck Anxiety Inventory (BAI) - Grade Point Average (GPA)	Statistically significant: - Increased knowledge of ADHD ($p<0.001$) - Increased use of organisational and other behavioural strategies ($p<0.001$) - Reduced levels of maladaptive thinking on CRT-A ($p<0.001$) - Reduced inattentive symptoms on CAARS-S:L ($p<0.001$) (moderate to large effect) - Reduction of total ADHD symptom on CAARS-S:L DSM-IV ADHD symptoms ($p<0.001$) (moderate to large effect) - Improvement across all executive function domains on BRIEF-A ($p<0.001$) (large effects) Not statistically significant: - Reduction of hyperactivity-impulsivity symptoms on CAARS-S:L DSM-IV hyperactive-impulsive symptoms ($p=0.054$) - Reduced levels of anxiety ($p=0.055$) - Reduced levels of depression ($p=0.134$) - Change in GPA

Author, year, country	Aims	Design	Participants	Intervention	Outcome measures	Findings and conclusion
Hartung <i>et al.</i> (2022), USA	To identify the effectiveness of a CBT intervention tailored specifically for college students with ADHD.	Open trial – before and after study (no comparison group) Authors do not report on registration nor Institutional Review Board approval. Participants providing informed consent was not reported.	30 students 20 UG; 8 GD; 2 PG 18-32 years old (M = 22.63 years old) 56.7% male 83.3% White/Non-Hispanic	New CBT intervention tailored specifically for college student with ADHD. 6 weeks - 6 group sessions - 3-6 individual sessions Main modules: - OTMP skills - Psychoeducation - Academic skills Setting - University-based psychology training clinics	- Social and Developmental History Form - DSM-5 Current Checklist, Self-Report - Weiss Functional Impairment Rating Scale, Self-Report (WFIRS) - Conners Adult ADHD Rating Scale, Self-Report, Long Version (CAARS-S:L) - Organizational, Time Management and Planning (OTMP), Self-Report	Adequate sample size to detect medium effect size. Statistically significant: - Reduction of inattentive ADHD symptoms on DSM-5 ADHD Symptoms Checklist ($p=0.006$) - Reduction of total ADHD symptoms on the CAARS DSM-IV ADHD Total Symptoms ($p=0.002$) (small to medium effect) - Decrease of impairment on the total WFIRS average score ($p=0.049$) and Self-Concept ($p=0.031$) domain (small to medium effect) - Increase in OTMP skill usage on the OTMP measure ($p=0.011$) (medium to large effect) Not statistically significant: - Reduction of hyperactive-impulsive symptoms on ADHD Symptoms Checklist.

Validity and reliability of the Thai Shortened Token Test

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ABSTRACT

Background: The Token Test (TT) helps evaluate language comprehension in individuals with aphasia. This test can detect comprehension difficulties, even in mild aphasia cases. In Thailand, the other language tests for aphasia focused primarily on multiple aspects of language, which took a long time to evaluate. The Shortened TT, which has fewer commands, has been chosen to be translated for this study. Previously, the Shortened TT was translated into Thai using only forward translation and had not yet been evaluated for its psychometric properties. Thus, this study focuses on translating the Shortened TT into Thai using a forward and backward translation process and determining its validity and reliability.

Objective: To translate, validate, and determine the reliability of the Thai Shortened TT.

Materials and methods: The Shortened TT was translated using forward and backward translation. Following the completion of the translation process, five expert speech-language pathologists (SLPs) evaluated its content validity using the Content Validity Index (CVI), the Content Validity Index for Items (I-CVI), and the Content Validity Index for Scales (S-CVI). Then, it was administered to 12 normal participants and 12 aphasia participants to determine the test-retest, intra-, and inter-rater reliability using the Intraclass Correlation Coefficient (ICC).

Results: The Thai Shortened TT's content validity was satisfied at CVI=0.920, I-CVI=0.800-1, and S-CVI=0.983. The test-retest, intra-, and inter-rater reliability were excellent. In the normal group, they were 0.943, 0.985, and 0.974, respectively; in the aphasia group, they were 0.985, 0.999, and 0.999, respectively.

Conclusion: This study indicated that the Thai Shortened TT can be utilized and is suitable for clinical evaluation regarding its content validity and reliability.

Introduction

Auditory comprehension deficiency is one of the symptoms in patients with aphasia. The loss of language and ability to comprehend others impacts the patient's quality of life.^{1,2} Aphasia may result from cerebrovascular disease, Traumatic Brain Injury (TBI), brain tumor, infection, dementia, or other neurodegenerative medical conditions. However, the most common cause of aphasia is cerebrovascular disease.³ In Thailand, the prevalence of cerebrovascular disease in populations over 45 is 1.88%.⁴ According to data, aphasia is the consequence of approximately 25-50% of all individuals with cerebrovascular disease.³

The Token Test (TT) is one of the assessments used to evaluate language comprehension in individuals with

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aphasia. This test can detect language comprehension difficulties in individuals with mild aphasia.⁵ The TT was developed by De Renzi and Vignolo in 1962.⁶ The test included 61 commands divided into five subtests, each containing instructions that increased in difficulty. The commands for subtest parts 1 through 4 comprised identical forms of verbs, nouns, and adjectives. Every subtest consisted of ten commands that were gradually extended. The final part of the test contained twenty-one commands with a more complex grammatical structure. Subjects must listen to the commands and execute tasks using tokens as responses. Ten circle tokens and ten rectangle tokens were present, each in two sizes (large and small) and five colors (red, blue, green, yellow, and white). As a result of the token usage, the test commands lacked any supplementary words that would aid understanding, including situation, object nature, or verbal context. The developers found that subjects with mild aphasia who demonstrated good language comprehension during communication struggled to respond to commands on the TT. They determined that TT can detect language comprehension deficiencies in patients with aphasia.⁶

The TT has been developed into various formats, such as the TT for Children (TTFC), the Revised TT (RTT), the Five-item RTT, and the Shortened TT.⁷⁻¹⁰

De Renzi and Faglioni subsequently developed the Shortened TT in 1978.⁷ In this version, the number of commands has decreased from 61 to 36. In the first through fourth parts, the number of orders decreased from 10 to 4, and in the final part, from 21 to 13. Furthermore, the developer designed a simple subtest comprising seven commands, all of which the subjects could accurately respond to on the condition that they understood the tokens' sizes, shapes, or colors. For example, once participants understood the definition of "circle," they could follow with the command "touch a circle." The tokens were converted from rectangles to squares due to their frequent usage. In addition, the blue tokens have been recolored to black because ordinary people and those with certain brain disorders would have difficulty distinguishing between green and blue.⁷ The Shortened TT, comprising 36 commands, was determined to be a sufficient tool for assessing language comprehension impairments in individuals with aphasia. This version of the TT was more frequently used in clinical settings.¹¹

The TT was translated into Thai using forward translation by Akamanon in 1989.¹² The Shortened TT was translated into 40 languages, including Thai, using forward translation for the application by Bastiaanse *et al.* in 2016.¹³ These two versions of the Thai-translated TT were translated only through forward translation and were not assessed for the test's psychometric properties. Gorecki *et al.* proposed using both forward and backward translation in an instrument translation process. Additionally, researchers must evaluate the test for its psychometric properties before using it.¹⁴ In 2016, Alkhamra and Al-Jazi translated TTFC into Arabic, utilizing forward and backward translation, and determined its validity and reliability.⁸

The study of the validity of the TT was conducted by Orgass and Poeck in 1966. This study determined the TT's criterion validity in healthy, non-aphasia brain-damaged, and aphasia participants. The results indicated that the validity of the test was not impacted by disorders resulting from brain injury, except aphasia. Healthy participants and those with non-aphasic brain injury scored significantly higher on the TT than participants with aphasia. To evaluate the test's efficacy, the researchers evaluated its discriminatory potential. They found that 84% of aphasic participants were accurately diagnosed with aphasia, while only 4% of non-aphasic participants were diagnosed with aphasia.¹⁵

In 2016, Alkhamra and Al-Jazi determined the construct and concurrent validity of the Arabic TTFC in Jordanian Arabic-native and bilingual children. The construct validity of the A-TTFC was evaluated using factor analysis. In accordance with the factor analysis findings, the A-TTFC items were comparable to the English version items. A two-factor mixed-effects model was employed to investigate concurrent validity. The ICCs between E-TFC and A-TTFC were more significant than 0.8.⁸

In 2000, Park *et al.* determined the test-retest, intra-, and inter-rater reliability of the Five-item RTT in aphasia participants.¹⁰ The study of the reliability of the Shortened TT was conducted by Paci *et al.* in 2015. This study determined the Shortened TT's intra- and inter-rater reliability in aphasia participants.¹⁶

The Shortened TT can detect language comprehension deficiencies in patients with aphasia, requiring less equipment, documentation, and time.⁷ The test must be translated using both forward and backward translation and be proven reliable and valid before it is used in clinics and research in the future.¹⁴ The aims of this current study were (a) to translate the Shortened TT into Thai by using forward and backward translation, (b) to determine its content validity, and (c) to examine its test-retest, intra-, and inter-rater reliability.

Materials and methods

This study was experimental research. Data were collected between May 2021 and December 2022 after approval from the Ramathibodi Hospital's ethical committee.

Procedures

The current study was divided into three steps: the test translation, the validity testing, and the reliability testing processes. The details are as follows:

Test translation

The Elsevier Copyright Clearance Center was contacted for authorization of the Shortened version of the TT translation because the author and corresponding author of the original study could not be reached. In this study, the Shortened TT was translated into Thai using forward and backward translation methods adapted from the guidelines of Gorecki *et al.*¹⁴ The translation steps consisted of (a) forward translation, (b) review of

the forward translation, (c) backward translation, and (d) review of the backward translation.

(a) Forward translation

The researcher and a certified speech-language pathologist (SLP) with at least three years of experience evaluating and training patients with aphasia carried out the forward translation from English to Thai. This step produced two sets of the Thai-translated test (the Thai Shortened TT version A and version B).

(b) Review of the forward translation

The review committee consisted of the two forward translators and another researcher. They compared two versions of the Thai-translated test to determine the meaning and usage of words. The forward translation phase was reviewed based on the following criteria: the language used in the test had to be natural and acceptable in Thai, and the test items had to maintain the original test's purpose.

(c) Backward translation

A professional translator in this step was a person with expertise in both languages from the Center for Translation and Language Services, Research Institute for Languages and Cultures of Asia (RILCA) at Mahidol University. The translator had no prior knowledge of the instrument. This step produced the backward-translated test (in English).

(d) Review of the backward translation

The review committee was comprised of two researchers and a backward translator from RILCA. The backward translated and original versions of the test were compared by identifying word meanings and usages that were consistent with the original version's concept. At this stage, the Thai Shortened TT was established.

This study could not conduct a pretesting phase in the test translation process due to the restrictions imposed by the coronavirus disease 2019 (COVID-19) on the number of patients, caregivers, and visitors at Ramathibodi Hospital who could participate in data collection.

Validity testing

Five experts, certified SLPs with at least 10 years of professional experience in assessing or training patients with aphasia, evaluated the content validity of the Thai Shortened TT. This study conducted the assessment of content validity using the Content Validity Index (CVI), the Content Validity Index for Item (I-CVI), and the Content Validity Index for Scale (S-CVI). The Thai Shortened TT was examined and compared to the original test's principles, including suggestions by the experts. Next, the Thai Shortened TT was revised.

Reliability testing

Participants

The participants in this study were recruited for the reliability testing process. They included patients, caregivers, and individuals who visited Ramathibodi

Hospital. They were adults who spoke Thai as their primary language and were at least 18 years old. The researcher would inform the participants of the research's purpose and explain the procedures. All participants signed or imprinted their fingerprints on the consent form to indicate their agreement to participate in this study.

The number of participants in this study was determined using the sample size requirement for an Intraclass Correlation formula.¹⁷ This formula considers the desired significance level ($\alpha=0.05$), statistical power (80%), and number of observations per subject set at 2, with $R_0=0$ and $R_1=0.7$. The calculation indicated a requirement of 10 participants per group. To account for potential withdrawals, the total number of participants increased by 20%, resulting in 24 participants divided into two groups: 12 participants with aphasia and 12 normal participants.

For aphasia participants, the inclusion criteria included: (a) having a history of cerebrovascular disease that a neurologist has diagnosed; (b) being evaluated and diagnosed with mild or moderate aphasia based on their aphasia quotient (AQ) score from the Thai Adaptation of the Western Aphasia Battery (T-WAB), which ranged from 40 points or above^{18,19} due to the subject that is considered severe if the score is less than this. The exclusion criteria were as follows: (a) had no correct responses in five consecutive items of the first part of the Thai Shortened TT, which resulted in the test's discontinuation; (b) they were unable to move their bodies in response to the test instructions due to restrictions on body movement.

For normal participants, the inclusion criteria were to have no history of cerebrovascular disease or communication disorders. The exclusion criteria included: (a) failure to meet the Mini-Mental State Examination-Thai 2002 (MMSE-Thai 2002) criteria, which is the subject that is illiterate and scored less than or equal to 14 points; the subject completed elementary school and scored less than or equal to 17 points; and the subject studied beyond elementary school and scored less than or equal to 22 points.²⁰ (b) had no correct responses in five consecutive items of the first part of the Thai Shortened TT. All participants had to have sufficient hearing to communicate, no visual or color blindness that could have restricted the assessment, and no previous history of mental health conditions.

The Thai Shortened TT was administered to the participants to determine the reliability of the test. Two raters participated in this procedure. The researcher served as the first rater, while a certified SLP with at least three years of experience in assessing and training individuals with aphasia served as the second rater. Before evaluating the participants, two raters were required to review the manual detailing assessment procedures and ratings. The first rater assessed the participants twice to determine the test-retest reliability. There were at least two weeks between each examination. The first rater assessed and recorded the video simultaneously during the initial assessment. These video recordings were later used to determine intra- and inter-rater reliability. After

the first rater assessed all the participants twice, the video records from the initial evaluation were randomized by another SLP to blind the groups of participants. The first rater reassessed the participants via video recording to determine the intra-rater reliability by comparing the scores from the initial evaluation with the scores rated via video recording. The second rater assessed the participants via the recorded video to determine inter-rater reliability by comparing the scores from the initial evaluation by the first rater. To avoid bias, the first rater did not participate in the scoring process when the second rater assigned the score.

Results

Validity testing

The content validity of the Thai Shortened TT was assessed by five expert SLPs, including CVI, I-CVI, and

S-CVI. The CVI, I-CVI, and S-CVI had the following defined criteria: (1) CVI>0.815²¹ or (2) I-CVI>0.78 and S-CVI>0.9.²²

The results revealed that the CVI=0.920, the I-CVI ranged from 0.800 to 1, and the S-CVI=0.983. These values met the criteria, and the test had a good validity result.

Reliability testing

Participants' characteristics

To determine the reliability of the Thai Shortened TT, this study included 12 aphasia participants and 12 normal participants. The participants' demographic information and scores on the MMSE-Thai 2002 and T-WAB were analyzed using descriptive statistics and presented as numbers of participants (percentages) or averages (standard deviation; SD). Table 1 presents the characteristics of the participants and the scores from T-WAB and MMSE-Thai 2002.

Table 1. Participants' characteristics.

	Number of participants (%)		
	Normal (N=12)	Aphasia (N=12)	Overall (N=24)
Gender			
Male	4 (33.3)	8 (66.7)	12 (50)
Female	8 (66.7)	4 (33.3)	12 (50)
Age			
Mean (SD)	57.8 (8.8)	58.8 (10.6)	58.3 (9.5)
Range	43-70	39-76	39-76
Education			
Elementary school	1 (8.3)	1 (8.3)	2 (8.3)
Junior high school	-	3 (25)	3 (12.5)
High school	2 (16.7)	-	2 (8.3)
Vocational certificate	1 (8.3)	-	1 (4.2)
Bachelor's degree	7 (58.3)	7 (58.3)	14 (58.3)
Postgraduate degree	1 (8.3)	1 (8.3)	2 (8.3)
AQ scores (T-WAB test)			
Mean (SD)	-	83.4 (14.2)	-
Range	-	61.8-99.6	-
Aphasia types			
Anomic aphasia	-	8 (66.7)	-
Transcortical sensory aphasia	-	2 (16.7)	-
Wernicke's aphasia	-	2 (16.7)	-
Duration of illness (month)			
Mean (SD)	-	51.4 (63.5)	-
Range	-	6-204	-
6-12 months		4 (33.3)	
13-24 months		3 (25)	
25-36 months		-	
37-48 months		1 (8.3)	
49-60 months		-	
61+ months		4 (33.3)	
MMSE-Thai 2002 scores			
Mean (SD)	27.5 (1.1)	-	-
Range	26-29	-	-

The test comprises 36 commands: 7 in part 1, 4 in parts 2 through 5, and 13 in part 6. The scoring procedure for parts 1-5 is as follows: 1 point is given if the subject performs the correct action during the first representation, 0.5 points if the subject performs the correct action after repeating the command, and 0 points if the subject fails to respond or responds incorrectly. The test is terminated if no correct answer is provided in parts 1-5 of the five

sequential items. In part 6, the subject receives 1 point if they offer the correct response and 0 points if they do not provide the proper response; the commands are not repeated in this part.⁷ The duration of the assessment is approximately 5 to 15 minutes.

This study conducted two assessments on-site and two via video recording to determine reliability. Table 2 displays the performance scores of each evaluation.

Table 2. The performance scores from the Thai Shortened TT in normal and aphasia groups.

	Normal group	Aphasia group
First assessment		
Mean (SD)	33.0 (1.9)	21.9 (10.0)
Range	28-35	5-33
Second assessment		
Mean (SD)	33.9 (1.9)	23.5 (10.6)
Range	30-36	8-35
Video assessment (Rater 1)		
Mean (SD)	32.9 (1.9)	22.1 (9.9)
Range	28-35	6-33
Video assessment (Rater 2)		
Mean (SD)	33.0 (2.0)	22.2 (9.9)
Range	28-35	5-33

The test-retest, intra-, and inter-rater reliability of the Thai Shortened TT was analyzed using intraclass correlation coefficients (ICCs) with a two-way mixed effects model. The ICC values were translated as follows: (1) The ICC value for which the instrument's reliability score was more significant than 0.90 indicated that it had excellent reliability; (2) between 0.75 and 0.90 was good reliability; (3) between 0.50 and 0.75 was moderate reliability; and

(4) less than 0.5 was poor reliability.²³

The test demonstrated excellent test-retest reliability, with ICC values ranging from 0.920 to 1 when compared to the criteria.²³ However, subtest part 1 in aphasia participants and all participants showed ICC=0.652 and 0.710, respectively, indicating moderate test-retest reliability and subtest part 5 in normal participants showed ICC=0.485, indicating poor test-retest reliability (Table 3).

Table 3. Test-retest reliability of the Thai Shortened TT.

	Normal		Aphasia		All	
	ICC (average)	95% CI	ICC (average)	95% CI	ICC (average)	95% CI
Overall	0.943	0.800-0.983	0.985	0.947-0.996	0.989	0.975-0.995
Part 1	1	-	0.652	-0.210-0.900	0.710	0.329-0.874
Part 2	1	-	0.920	0.723-0.977	0.926	0.825-0.967
Part 3	1	-	0.990	0.670-0.997	0.992	0.981-0.997
Part 4	1	-	0.980	0.931-0.994	0.986	0.969-0.994
Part 5	0.485	-0.789-0.852	0.937	0.781-0.981	0.957	0.900-0.981
Part 6	0.963	0.871-0.989	0.958	0.854-0.988	0.974	0.939-0.989

The test showed excellent intra-rater reliability, with ICC values ranging from 0.946-1 compared to the criteria (Table 4).²³

The test displayed excellent inter-rater reliability, with ICC values ranging from 0.966-1 when compared to the criteria (Table 5).²³

Table 4. Intra-rater reliability of the Thai Shortened TT.

	Normal		Aphasia		All	
	ICC (Average)	95% CI	ICC (Average)	95% CI	ICC (Average)	95% CI
Overall	0.985	0.948-0.996	0.999	0.998-0.999	0.999	0.998-0.999
Part 1	1	-	0.946	0.812-0.984	0.955	0.895-0.980
Part 2	1	-	0.995	0.982-0.998	0.995	0.988-0.998
Part 3	1	-	0.994	0.979-0.998	0.995	0.988-0.998
Part 4	1	-	1	-	1	-
Part 5	1	-	1	-	1	-
Part 6	0.980	0.932-0.994	0.998	0.993-0.999	0.997	0.993-0.999

Table 5. Inter-rater reliability of the Thai Shortened TT.

	Normal		Aphasia		All	
	ICC (Average)	95% CI	ICC (Average)	95% CI	ICC (Average)	95% CI
Overall	0.974	0.911-0.993	0.999	0.996-0.999	0.999	0.997-0.999
Part 1	1	-	1	-	1	-
Part 2	1	-	0.995	0.982-0.998	0.995	0.988-0.998
Part 3	1	-	0.993	0.976-0.998	0.994	0.987-0.998
Part 4	1	-	0.969	0.892-0.991	0.979	0.951-0.991
Part 5	1	-	1	-	1	-
Part 6	0.966	0.883-0.990	0.996	0.985-0.999	0.996	0.990-0.998

Discussion

Validity

This study examined the content validity of the Thai Shortened TT. Nevertheless, it did not examine the same type of validity as other studies.^{8,15} Its content validity analysis revealed that the CVI, I-CVI, and S-CVI values met the criteria.^{21,22} The Thai Shortened TT items were modified based on the experts' recommendations. In this phase, the adjustments were made while maintaining the contents of the original test and its appropriateness for the characteristics of the Thai language. For example, the instructions for items 24, 28, 30, and 32 were changed from "place" to "pick up and place" by adding the word "หยิบ" (meaning "pick up") to clarify the actions in the instructions. These modifications were aimed at making the instructions more explicit and more precise.

Reliability

The test-retest reliability result of this study, ICC=0.974, was comparable to the study of Park *et al.*,¹⁰ showing excellent test-retest reliability. The study also demonstrated excellent test-retest reliability with the five-item RTT, with ICC=0.96.¹⁰ However, the test-retest reliability of the fifth subtest of the Thai Shortened TT was low among normal participants, with ICC=0.485. Although the details of these two tests varied, the format of some subtest items was similar. The items in the fifth subtest

of the Thai Shortened TT were grammatically equivalent to those in the fourth subtest of the five-item RTT, which had moderate test-retest reliability, ICC=0.73.¹⁰ Variations in the methodology details could explain the difference in test-retest reliability. The participants and the time intervals between the two examinations in this study and of Park *et al.* were different. Park *et al.*'s study only included participants with aphasia,¹⁰ while this study included both aphasia and normal participants. The interval between the two examinations in this study was two weeks, while Park *et al.*'s study was three days.¹⁰ Park *et al.* suggest that the participants' learning or changes in individual ability may cause this low test-retest reliability.¹⁰ Additionally, low test-retest reliability may be associated with the duration of the two assessments,²⁴ the lack of variability among the sampled subjects, and the small number of subjects.²³

The Thai Shortened TT's intra- and inter-rater reliability were excellent, ICC=0.997 and 0.996, compared to the study of Park *et al.*, which showed that the five-item RTT also demonstrated excellent intra- and inter-rater reliability, ICC=0.98 and 0.95.¹⁰ Like the study of Park *et al.*, the video recordings of the initial assessment were used in this phase. Additionally, the Park *et al.* study raters received training in assessment and rating before the participant assessments.¹⁰ This study also gave the raters a manual defining the assessment procedures and scoring details. The methodology of this study was like that of Park

et al., which could explain why its results were comparable to theirs.

On the other hand, this study's intra- and inter-rater reliability results differ from those of Paci *et al.*¹⁶ In that study, the Shortened TT showed good intra-rater reliability, ICC=0.889, and moderate inter-rater reliability, ICC=0.588. Two evaluations were conducted on their participants, with a minimum of two days between each evaluation. Their raters weren't provided training or a manual for evaluating and scoring. In their conclusion, Paci *et al.* suggested that the minimal reliability values may be associated with participants' learning or changes in individual competence. They also indicated that explicit scoring guidelines and instructions on conducting the testing procedure could enhance the test's reliability.¹⁶

Conclusion

This study aimed to translate, validate, and assess the reliability of the Thai Shortened TT. Begin by translating the Shortened TT into Thai using both forward and backward translation processes. Five expert SLPs assessed the Thai Shortened TT's content validity. Based on the results, this test's content validity met the criteria. This test's intra-, inter-rater, and test-retest reliability were evaluated in normal and aphasia participants using ICCs. According to the results, this test showed excellent intra-, inter-rater, and test-retest reliability. Consequently, this test is suitable for clinical evaluation and future research.

Limitations

During the backward translation phase, the translator had to be proficient in the target language and use the original language as their mother tongue. Due to difficulties in finding the required translator, the translator was a professional translator with expertise in both languages from the Center for Translation and Language Services, RILCA, Mahidol University, Nakhon Pathom, Thailand.

The backward translation phase review committee was required to consist of the test's developer and forward translators. However, the original study's author and corresponding author could not be contacted. Therefore, the review committee for this study consisted of two researchers and the backward translator from RILCA.

This study did not conduct the pretesting phase of the translation procedure due to the COVID-19 pandemic during data collection.

Recommendations

The English version has cut-point data, which is a score of less than 29 points; the subject has an auditory comprehension deficit.⁷ Future research should establish normative or cut-point data for the Thai version, which is necessary to make this test suitable for screening the Thai population.

If sufficient individuals are available to participate in the study that translates to other tests, a pretesting phase should be conducted. If possible, the backward translator should be a native speaker of the test's original

language, have experience in the target language, and live in a country that uses it; furthermore, if they could be contacted, the translation would need to be returned to the original test developer for review.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The present study received approval from the Ethical Committee of the Ramathibodi Hospital, COA. No. MURA2021/455.

References

- [1] Hallowell B. Aphasia and other acquired neurogenic language disorders: a guide for clinical excellence. San Diego, CA: Plural Publishing, Inc; 2017.
- [2] Babkair LA, Chyun D, Dickson VV, Almekhlafi MA. The effect of psychosocial factors and functional independence on poststroke depressive symptoms: a cross-sectional study. *J Nurs Res.* 2022; 30(1). doi: 10.1097/JNR.0000000000000464.
- [3] American Speech-Language-Hearing Association. Aphasia [cited 2024 Sep 9]. Available from: <https://www.asha.org/practice-portal/clinical-topics/aphasia>.
- [4] Suwanwela NC. Stroke epidemiology in Thailand. *J Stroke.* 2014;16(1):1-7. doi: 10.5853/jos.2014.16.1.1.
- [5] Spreen O, Risser AH. Assessment of aphasia. New York: Oxford University Press; 2003.
- [6] De Renzi E, Vignolo LA. The token test: a sensitive test to detect receptive disturbances in aphasics. *Brain.* 1962; 85(4): 665-78. doi: 10.1093/brain/85.4.665.
- [7] De Renzi E, Faglioni P. Normative data and screening power of a shortened version of the token test. *Cortex.* 1978; 14(1): 41-9. doi: 10.1016/s0010-9452(78)80006-9.
- [8] Alkhamra RA, Al-Jazi AB. Validity and reliability of the Arabic Token Test for children. *Int J Lang Commun Disord.* 2016;51(2):183-91. doi: 10.1111/1460-6984.12198.
- [9] Arvedson J, McNeil M, West TL. Prediction of revised token test overall, subtest, and linguistic unit scores by two shortened versions. *Proceedings of 15th Clinical Aphasiology Conference*; 1985 Jun 2-6; Ashland, Oregon, 1985. Available from: <http://aphasiology.pitt.edu/838>.
- [10] Park GH, McNeil MR, Tompkins CA. Reliability of the five-item revised token test for individuals with aphasia. *Aphasiology.* 2000;14(5-6): 527-35. doi: 10.1080/026870300401298.
- [11] Hall J, O'Carroll RE, Frith CD. Neuropsychology. In: Johnstone EC, Owens DC, Lawrie SM, McIntosh AM, Sharpe M, editors. *Companion to psychiatric studies*.

- 8th Ed. St. Louis: Churchill Livingstone; 2010.
- [12] Akamanon C. The assessment of auditory comprehension ability with a Thai adaptation of the token test. *Rama Med J.* 1989; 12: 104-8. (in Thai).
- [13] Bastiaanse R, Raaijmakers S, Satoer D, Visch-Brink E. The multilingual token test. *Aphasiology.* 2016; 30(4): 508. doi: 10.1080/02687038.2015.1121710.
- [14] Gorecki C, Brown JM, Briggs M, Coleman S, Dealey C, McGinnis E, et al. The Pressure ulcer quality of life (PU-QOL) questionnaire, Language translation & cross-cultural adaptation guideline. [e-book] Leeds: University of Leeds; 2014 [cited 2021 Apr 16]. Available from: https://ctr.leeds.ac.uk/wp-content/uploads/2019/01/Translation_Guidelines_10JAN14_finalv1.0.pdf
- [15] Orgass B, Poeck K. Clinical validation of a new test for aphasia: an experimental study on the token test. *Cortex.* 1966; 2(2): 222-43. doi: 10.1016/S0010-9452(66)80005-9.
- [16] Paci M, Lorenzini C, Fioravanti E, Poli C, Lombardi B. Reliability of the 36-item version of the token test in patients with poststroke aphasia. *Top Stroke Rehabil.* 2015; 22(5): 374-6. doi: 10.1179/1074935714Z.0000000049.
- [17] Bujang MA. A simplified guide to determination of sample size requirements for estimating the value of intraclass correlation coefficient: a review. *Arch Orofac Sci.* 2017; 12: 1-11.
- [18] Teerapong W. The comparison of language abilities of Thai aphasic patients and Thai normal subjects by using Thai adaptation of western aphasia battery [MA Thesis]. Bangkok: Mahidol University. 2000.
- [19] Kauhanen M-L, Korpelainen JT, Hiltunen P, Määttä R, Mononen H, Brusin E, et al. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovasc Dis.* 2000; 10(6): 455-61. doi: 10.1159/000016107. PMID: 11070376.
- [20] The Committee prepared the Preliminary Brain Test-Thai version. Mini mental examination Thai-2002, MMSE-2002. Bangkok: Institute of Geriatric Medicine, Department of Medical Services, Ministry of Public Health, Thailand; 2002. (in Thai).
- [21] Srisatidnarakul B. Development and validation of research instruments: Psychometric properties. Chulalongkorn University Printing House: Bangkok; 2012. (in Thai).
- [22] Polit DF, Beck CT. The content validity index: are you sure you know what's being reported? Critique and recommendations. *Res Nurs Health.* 2006; 29(5): 489-97. doi: 10.1002/nur.20147.
- [23] Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016; 15(2): 155-63. doi: 10.1016/j.jcm.2016.02.012.
- [24] Meehanpong P, Boonsin S. The development of nursing research instruments. *Journal of The Royal Thai Army Nurses.* 2021; 22(1): 10-9. (in Thai). <https://he01.tci-thaijo.org/index.php/JRTAN/article/view/242019>.

Appendix

A sample of the commands in the Thai Shortened Token Test

Part 1

1. ตะวงกลมอันหนึ่ง
2. ตะสี่เหลี่ยมอันหนึ่ง

Part 2

1. ตะสี่เหลี่ยมเหลือง
2. ตะวงกลมดำ

Part 3

1. ตะวงกลมเล็กขาว
2. ตะสี่เหลี่ยมใหญ่เหลือง

Part 4

1. ตะวงกลมแดงและสี่เหลี่ยมเขียว
2. ตะสี่เหลี่ยมเหลืองและสี่เหลี่ยมดำ

Part 5

1. ตะวงกลมใหญ่ขาวและสี่เหลี่ยมเล็กเขียว
2. ตะวงกลมเล็กดำและสี่เหลี่ยมใหญ่เหลือง

Part 6

1. หีบวงกลมแดงวางไว้บนสี่เหลี่ยมเขียว
2. ตะวงกลมดำด้วยสี่เหลี่ยมแดง

Note: This test is part of the Mahidol University thesis. To obtain authorization to use the test, please contact Mahidol University or the first author by this email: ntrisakdipol@gmail.com for more information.



Review article: Designing grid displays in AAC systems to enhance accuracy and reduce latency in symbol searching

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ABSTRACT

Augmentative and Alternative Communication (AAC) systems support individuals with complex communication needs. This review article examines factors influencing the design of grid displays in AAC systems to enhance symbol searching accuracy and reduce latency. Four key areas are identified: the organization of symbols, color cues, visual crowding, and symbol location. Effective symbol organization, such as semantic-syntactic and schematic displays, can facilitate efficient communication, while color cues may improve visual attention and memory recall. Managing visual crowding and strategically placing symbols based on visual field biases and motor control abilities are also crucial. By optimizing these elements, speech-language pathologists can develop AAC displays that improve user communication outcomes. The findings provide guidelines for designing user-centered AAC systems tailored to individual cognitive, motor, and sensory needs.

Introduction

Augmentative and alternative communication (AAC) is a field of clinical practice that serves the demands of individuals with complex communication needs, which are defined by deficiencies in an expressive mode (e.g., speaking and writing) and/or a receptive mode of communication (e.g., spoken language comprehension). The communication competence of those individuals fails to meet their communication needs in various circumstances (e.g., communicating with unfamiliar communication partners and/or environments, noisy environments, group talking, etc.). The impairments that feasibly result in complex communication needs may include congenital disabilities (e.g., cerebral palsy, developmental apraxia of speech, etc.), acquired disabilities (e.g., amyotrophic lateral sclerosis, stroke, etc.), or neurological differences (e.g., autistic spectrum disorders, down syndrome, etc.).^{1,2}

There are two main types of AAC systems: Unaided and aided. Unaided systems involve AAC modes that do not require an external tool. These systems include gestures, vocalizations, finger spelling, manual signs, facial expressions, etc. Aided systems, on the other hand, require external tools. These systems include writing, photographs, natural objects, communication boards, etc. Aided systems also come in three forms: low-tech (i.e., nonelectronic AAC forms), such as writing, natural objects, and communication boards; mid-tech (i.e., battery-powered electronic AAC forms), such as single-button-communication switches and GoTalk³, and high-tech (i.e., electronic AAC

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forms with more advanced processors) such as Tablet-based speech-output technologies and speech generating devices.^{1,2}

There are two significant types of display layout used in picture-based AAC systems (e.g., communication boards/books, drawings (or line drawings), speech-generating devices, etc.): Visual scene display (VSD) and grid. VSD embedded vocabulary concepts within natural scenes (i.e., typically photographs) according to each AAC user's life. Vocabulary words are represented in pictures, and vocabulary words in each category are grouped in each scene.⁴⁻⁶ For example, in the kitchen scene, vocabulary words such as stove, kettle, fridge, cooking, and hungry are embedded. In contrast, the grid layout presents vocabulary words as graphic symbols arranged in rows and columns in a grid pattern. Each grid contains a single graphic symbol and is isolated in physical space.²

Different display layouts may influence the efficiency of AAC for communication. For instance, it has been reported that VSD is more uncomplicated to learning than grid layout for beginning communicators and young children.⁷⁻¹⁰ The AAC display's design should promote users' ability to communicate. Communication proficiency may include the user's motivation,^{11,12} vocabulary words corresponding to their needs and interests,² communication speed and accuracy,^{2,13-15} and other factors. To design the AAC display to support communication competence, many research studies revealed that the display should be created by the individual's cognitive/linguistic, literacy, motor, sensory, and perceptual abilities.¹⁶⁻¹⁸ Otherwise, an unsuitable AAC display design might impose additional demands on users to create messages, leading to challenges and frustration for the user and communication partners.¹⁹

The latency and accuracy of symbol searching are among the key factors significantly contributing to

AAC users' communication effectiveness. Many studies have explored the elements that impact the latency and accuracy of symbol searching. This review article intends to report and summarize the factors in designing the grid displays that enhance AAC users' latency and accuracy, providing a guideline for speech-language pathologists. According to the review, there are four primary areas of research interest related to symbol searching latency and accuracy when designing grid displays: (a) Strategies for organizing symbols, (b) Color of symbols, (c) Visual crowding, and (d) Location of symbols.

Strategies for organizing symbols

This domain concerns how symbols are arranged on a page to facilitate efficient symbol searches. Currently, there are seven types of symbol organization: (a) Semantic-syntactic, (b) Schematic, (c) Taxonomic, (d) Pragmatically organized displays, (e) Alphabetical, (f) Chronological, and (g) Idiosyncratic. Each type possesses distinct characteristics, necessitating careful decision-making to match the organization to individuals' abilities and preferences. For example, Burke, Beukelman, and Hux reported that participants with traumatic brain injury (TBI) preferred to use schematic grid displays despite showing better communication competency when using alphabetic grid displays.²⁰

A semantic-syntactic grid displays organized symbols according to syntactic functions (i.e., part of speech). Each page contains various types of words. Following Fitzgerald's Key Format, subjects, verbs, adjectives, objects, places, times, and so on are arranged from left to right, respectively.²¹ This organization is designed to promote language learning in individuals with complex communication needs.² The depiction of semantic-syntactic grid displays is shown in Figure 1.



Figure 1. Semantic-syntactic grid displays.

The symbols were sourced from ARASAAC and designed by Sergio Palao.

Schematic grid displays, also called activity grid displays, organize symbols based on activity themes such as routines, zoo visits, birthday parties, gardening, and other activities. Each page includes nouns (e.g., people, places, animals, plants), verbs, and prepositions related to the theme. An example of a schematic grid display is shown in Figure 2. Research studies suggest that schematic grid displays facilitate AAC symbol learning.^{22,23} However, there are two main disadvantages to this type of display. First, the exact vocabulary words may

repeatedly appear on different pages, leading to increased memory load in high-tech devices (e.g., smartphones and tablets) and added weight in low-tech AAC forms (e.g., communication boards). Second, this arrangement reduces the automaticity of learning using the AAC system, as users must individually learn the different locations of the target word (i.e., symbol) on each schematic page. It is recommended that schematic pages be combined with semantic-syntactic grid displays.²

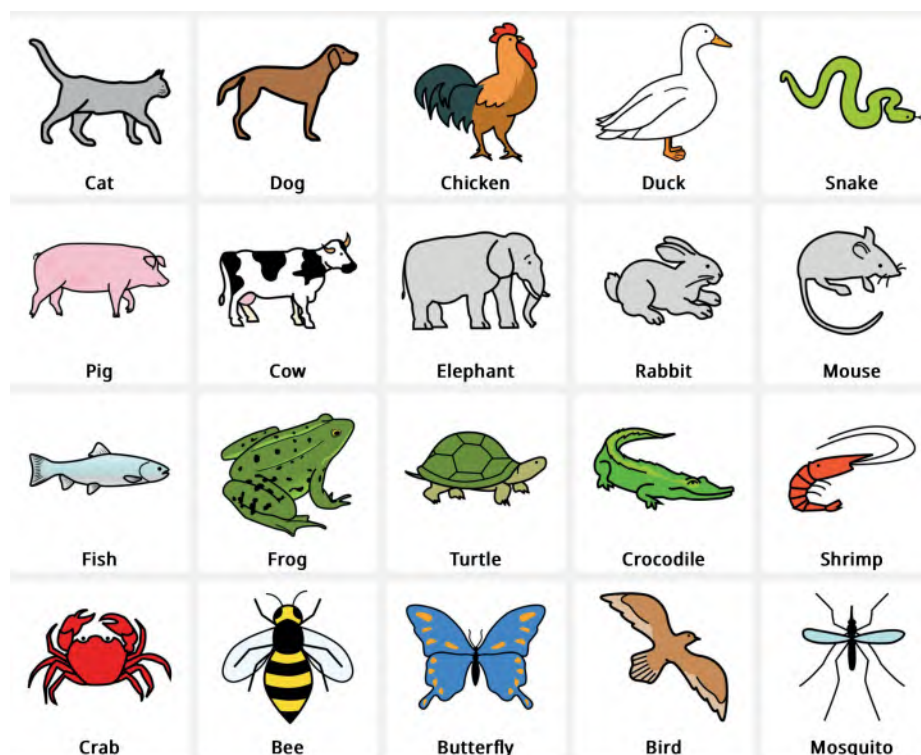


Figure 2. The schematic grid displays the animal theme.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The taxonomic grid displays symbols in categories such as fruits, animals, family members, places, clothes, action words, and so on. This type of display requires users to comprehend the concept of categorization, making it unsuitable for individuals younger than six or seven years old.²⁴ Furthermore, taxonomic grid displays have a significant drawback, as they necessitate extensive navigation between pages to find target words. Consequently, this display format may be appropriate for individuals with complex communication needs who use AAC to supplement their speech to clarify specific words rather than relying on AAC as their primary means of communication.²

Pragmatically organized displays incorporate multiple types of display organization to mitigate the limitations of each type, such as the time-consuming

nature of searching for target symbols. By integrating semantic-syntactic, taxonomic, and schematic grid displays, the time spent searching for symbols within specific conversational contexts—such as discussing a visit to the zoo—can be reduced. Examples of systems using this type of organization include Pragmatic Organization Dynamic Displays (PODD), Voco Chat, and Snap Core First, each offering unique features.²⁵ For instance, PODD is the inclusion of a navigation page, which directs users to the target symbols through page tabs such as the main page (i.e., semantic-syntactic), food category (i.e., taxonomic), ordering food (i.e., schematic), conversational repair (i.e., taxonomic), and so on. An example of PODD is illustrated in Figure 3. The primary disadvantage of this type of display is the potential for the exact words or symbols to appear repeatedly across multiple pages.²



Figure 3. Starter page of Pragmatic Organization Dynamic Displays (PODD).
The symbols were sourced from ARASAAC and designed by Sergio Palao.

An alphabetic grid displays organized symbols in alphabetical order. For instance, the first page contains words starting with “A,” and the second page includes words beginning with “B,” and so forth. This organization may be appropriate for literate individuals. Moreover, this display format might be ideal for individuals with complex communication needs who use AAC to enhance their speech by clarifying specific words rather than using AAC as their primary mode of communication.²

Chronological grid displays, also known as visual schedules or calendar systems, organize activities in sequential order, either in rows or columns. This arrangement helps individuals follow a structured sequence of tasks, reducing challenging behaviors that may arise during activity transitions. An example of a chronological grid display is Figure 4.

Idiosyncratic grid displays are personalized arrangements of symbols tailored to an individual’s unique preferences, needs, or interests that fit their cognitive organization or abilities, such as organizing by favorite movies, personal pets, etc. These displays are customized to align with the user’s communication style and requirements.²



Figure 4. Chronological grid displays related to the morning routine.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

Color of the symbols

Many cognitive factors affect how successfully AAC users employ grid display, but visual cognition is the factor that contributes most in terms of grid display.²⁶⁻²⁸ Visuospatial processing is considered the primary skill needed to use visually-based aided AAC systems.²⁶ Visuospatial processing is integral visual skills, including symbol perception (i.e., the ability to notice the presence of a symbol on a display), symbol discrimination (i.e., the ability to distinguish between two symbols on a display), identification (i.e., the ability to recognize what a symbol represents), and recall (i.e., ability to remember where the symbol is located on display).^{26,27} Individuals with developmental and intellectual disabilities frequently experience difficulty inhibiting their attention to distracting stimuli.^{29,30} This challenge may be related to issues about visuospatial processing, especially visuospatial working memory.^{30,31} To reduce this issue, researchers examine the effects of color cues on symbol learning in children with and without disabilities.

Research has shown that the use of color can have a positive impact on processing and aiding the learning of symbol meaning for children with multiple disabilities.^{26, 32-34} These findings were supported by evidence that color facilitates image retrieval.^{26,35,36} Visual short-term memory may be improved when distinct colors represent different features of an object.³⁷ Long-term visual memory is strengthened when specific colors and forms are associated with memory representation.³⁵ In addition, Párraga *et al.* indicated that color can influence attention and enhance perception speed.³⁸ Therefore, numerous studies have investigated the impact of color on attention and the speed of target symbol searching, focusing on two primary aspects: the internal symbol color and the symbol

background color.

Internal symbol color attracts attention, differentiates between similar objects, and facilitates object recognition.³⁹ Moreover, surface color can aid in the grouping of objects.⁴⁰ According to these findings, many researchers intended to investigate whether the internal symbol color could increase the speed and accuracy of locating the symbol in grid displays when the like-colored symbols were grouped. Most research outcomes showed that grouping symbols with similar colors improves the efficiency of finding the symbol in the array.⁴¹⁻⁴⁵ This might be because clustering like-colored symbols decreases cognitive load and enhances visual attention.^{41,42,44,46}

For example, Wilkinson and Madel measured the gaze pattern of six children with Down syndrome and six children with autism by using eye-tracking technology. The results demonstrated that participants significantly focused on target symbols while fixating less on distractors when the like-colored symbols were clustered together. An example of internal color cues with a clustering arrangement is illustrated in Figure 5. Nevertheless, Hetzroni and Ne'eman's research findings indicated that all four preschoolers with autism showed no differences in success in learning recognition of the new vocabulary, regardless of the level of color (i.e., grey-scale symbols versus color symbols) included in the symbols.⁴⁷ Although clustering symbols on the array that shared internal color could improve symbol searching accuracy and reduce latency, there was a notable limitation. The number of symbols that do not share the same internal color makes it impossible to arrange them by clustering based on internal color. Consequently, some researchers explored the effects of background color cues on the accuracy and latency of the symbol-searching process.

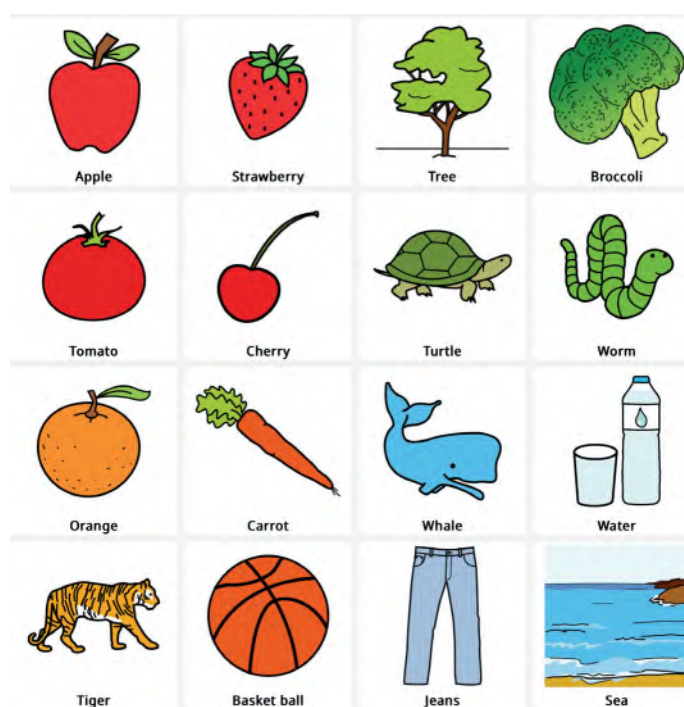


Figure 5. Internal color cues with a clustering arrangement.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The influence of symbol background color was examined concerning two primary effects: (a) the speed of identifying individual symbols functioning as a semantic cue, and (b) the speed of identifying a sequence of symbols (i.e., for constructing multi-symbol messages) functioning as a syntactic cue. Most research studies have shown that background color cues do not improve the speed or accuracy of single symbol searching in children with typical development^{43,48,49} or Down syndrome.⁵⁰ For example, Wilkinson and Snell investigated whether background color cueing helps children with typical development identify emotion symbols grouped by valence. The results indicated that background color did not enhance the children's ability to identify symbols more quickly.⁴⁹ These studies reported that background color cues related to semantics neither provided any advantage in searching nor slowed down the process of locating a single symbol due to the distracting effect. However, One study demonstrated that symbol background color increased the speed of single symbol searching in adults without disabilities and recommended using background color cues with communication partners to assist individuals who rely on AAC in locating target symbols on a grid display.⁵¹

Likewise, in terms of using background colors as a syntactic cue (e.g., word-class categories such as red background for pronouns, blue background for action verbs, yellow background for adverbs, etc.), studies reported that background color cues did not aid multi-symbol message construction in young children. This might be because background color cueing as a syntactic cue might be linked to metalinguistic skills, typically emerging between 5 and 7 years of age.⁵² Therefore, employing background color cueing to enhance sentence construction may only benefit older individuals with intact metalinguistic awareness.⁵¹ However, Wilkinson et al. reported that background color cueing reduced the latency in locating the target symbol. This may be attributed to the fact that the participants in the study were adults with Down syndrome, whose average receptive vocabulary age was approximately 7 years and 0 months.⁵³ The illustration of using background-color cueing as a syntactic cue is shown in Figure 1.

The impact of background color cues remains a subject of ongoing research. The researchers suggest that the lack of benefit from background color cues in young children may be due to the increased cognitive load imposed by the need to interpret the color cues, a skill that young children may not yet possess.⁴⁹ This aligns with Wilkinson and Jagaroo's assertion that the effectiveness of color cues depends on the user's cognitive abilities and the complexity of the visual display.²⁶

Visual crowding

Visual crowding or clutter refers to a phenomenon where symbols become indistinguishable due to proximity. In a standard grid display, multiple rows and columns of symbols are arranged adjacently, without intervening space, and with uniform dimensions. This configuration leads to difficulties in distinguishing individual elements, limits eye and hand movement, and impedes visual

search efficiency.^{19,54} The recognition of an object is hindered when the spacing between objects is too narrow, particularly for objects that are not centrally located.⁵⁵ Wilkinson et al. conducted a study to evaluate the impact of visual crowding across four different arrangement conditions (i.e., closed-set grid, widely spaced grid, perimeter, and corners) on latency and fixation to distractors. In each arrangement, symbols were grouped according to grammatical categories, including subjects, actions, objects, and descriptors. The results indicated that participants with Down syndrome were less likely to fixate on irrelevant symbols when the symbols were more widely spaced. However, reducing visual crowding did not lead to an improvement in the latency of symbol searching.⁵³

Location of symbols

According to research studies, symbol location is influenced by two key aspects: visual field biases and motor control ability. Visual field biases can impact visual-spatial performance, leading individuals to attend to one-half of the visual field preferentially.^{56,57} For instance, individuals with left-hemisphere dominance often focus more on the right visual field.⁵⁸ Moreover, research indicates that symbols with abstract forms are best positioned on the right side of the display,⁵⁹ whereas symbols depicting emotional facial expressions and geometric configurations are more effectively placed on the left side.^{60,61}

Furthermore, an individual's motor control ability must be assessed to position symbols optimally, ensuring easier access. Beukelman and Light provided an example where frequently used symbols are placed on the side of the display that corresponds to the hand with better motor control.²

Conclusion

The effectiveness of communication for AAC users is significantly influenced by the latency and accuracy of symbol searching. This review article has summarized vital factors that contribute to these aspects, focusing on the design of grid displays that enhance symbol searching efficiency. The primary areas of interest include the organization of symbols, the use of color, visual crowding, and the location of symbols on the grid. By understanding and applying these factors, speech-language pathologists can create more effective AAC systems that improve user communication outcomes. The research highlights the importance of strategic symbol arrangement, appropriate color cues, managing visual crowding, and considering individual visual and motor control abilities in designing grid displays. These insights provide a valuable guideline for optimizing AAC tools to better support users with complex communication needs.

References

- [1] Association AS-L-H. Augmentative and alternative communication (AAC) [cited 2024 July 20]. Available from: <https://www.asha.org/practice-portal/professional-issues/augmentative-and-alternative-communication/>.

- [2] Beukelman D, Light J. Augmentative and alternative communication: Supporting children and adults with complex communication needs. 5th Ed. Pennsylvania: Paul H. Brookes Publishing; 2020.
- [3] Desch LW, Gaebler-Spira D, Council on children with disabilities. Prescribing assistive-technology systems: Focus on children with impaired communication. *Pediatrics*. 2008; 121(6): 1271-80. doi:10.1542/peds.2008-0695.
- [4] Blackstone S, Light J, Beukelman D, Shane H. Visual scene displays. *Augment Comm News*. 2004; 16(2): 1-6.
- [5] Wilkinson KM, Light J. Preliminary investigation of visual attention to human figures in photographs: Potential considerations for the design of aided AAC visual scene displays. *J Speech Lang Hear Res*. 2011; 54(6): 1644-57. doi:10.1044/1092-4388(2011/10-0098).
- [6] Dietz A, McKelvey M, Beukelman DR. Visual scene displays (VSD): New AAC interfaces for persons with aphasia. *Perspect Augment Altern Commun*. 2006; 15(1): 13-7. doi: 10.1044/aac15.1.13.
- [7] Drager KD, Light JC, Speltz JC, Fallon KA, Jeffries LZ. The performance of typically developing 2½-year-olds on dynamic display AAC technologies with different system layouts and language organizations. *J Speech Lang Hear Res*. 2003; 46(2): 298-312. doi: 10.1044/1092-4388(2003/024).
- [8] Drager KD, Light JC, Carlson R, D'Silva K, Larsson B, Pitkin L, Stopper G. Learning of dynamic display AAC technologies by typically developing 3-year-olds. *J Speech Lang Hear Res*. 2004; 47(5): 1133-48. doi: 10.1044/1092-4388(2004/084).
- [9] Drager KD, Light J, Currall J, Muttiah N, Smith V, Kreis D, Nilam-Hall A, Parratt D, Schuessler K, Shermetta K, Wiscount J. AAC technologies with visual scene displays and "just in time" programming and symbolic communication turns expressed by students with severe disability. *J Intellect Dev Disabil*. 2019; 44(3): 321-36. doi: 10.3109/13668250.2017.1326585.
- [10] Holyfield C, Caron JG, Drager K, Light J. Effect of mobile technology featuring visual scene displays and just-in-time programming on communication turns by preadolescent and adolescent beginning communicators. *Int J Speech Lang Pathol*. 2019; 21(2): 201-11. doi: 10.1080/17549507.2018.1441440.
- [11] Higginbotham DJ, Shane H, Russell S, Caves K. Access to AAC: Present, past, and future. *Augment Altern Commun*. 2007; 23(3): 243-57. doi: 10.1080/07434610701571058.
- [12] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Positioning students with cerebral palsy to use augmentative and alternative communication. *Lang Speech Hear Serv Sch*. 1990; 21(1): 15-21. doi: 10.1044/0161-1461.2101.15.
- [13] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Hierarchy of conversational rule violations involving utterance-based augmentative and alternative communication systems. *Augment Altern Commun*. 2008; 24(2): 149-61. doi: 10.1080/07434610802038288
- [14] McCoy KF, Bedrosian JL, Hoag LA, Johnson DE. Brevity and speed of message delivery trade-offs in augmentative and alternative communication. *Augment Altern Commun*. 2007; 23(1): 76-88. doi: 10.1080/07434610600924515.
- [15] Todman J. Rate and quality of conversations using a text-storage AAC system: Single-case training study. *Augment Altern Commun*. 2000; 16(3): 164-79. doi: 10.1080/07434610012331279024.
- [16] Blackstone S. Designing displays: Hints and examples. *Augment Comm News*. 1993; 6(1): 1-6.
- [17] Light J, Lindsay P. Cognitive science and augmentative and alternative communication. *Augment Altern Commun*. 1991; 7(3): 186-203. doi: 10.1080/07434619112331275893.
- [18] Johnson JM, Inglebret E, Jones C, Ray J. Perspectives of speech language pathologists regarding success versus abandonment of AAC. *Augment Altern Commun*. 2006; 22(2): 85-99. doi: 10.1080/07434610500483588.
- [19] Light J, Wilkinson KM, Thiessen A, Beukelman DR, Fager SK. Designing effective AAC displays for individuals with developmental or acquired disabilities: State of the science and future research directions. *Augment Altern Commun*. 2019; 35(1): 42-55. doi: 10.1080/07434618.2018.1558283
- [20] Burke R, Beukelman DR, Hux K. Accuracy, efficiency and preferences of survivors of traumatic brain injury when using three organization strategies to retrieve words. *Brain Inj*. 2004; 18(5): 497-507. doi: 10.1080/02699050310001645784.
- [21] Fitzgerald E, editor. Straight language for the deaf. In: *Proceedings of the Twenty-Eighth Meeting of the Convention of American Instructors of the Deaf*; 1933; West Trenton, New Jersey.
- [22] Dada S, Huguet A, Bornman J. The iconicity of picture communication symbols for children with English additional language and mild intellectual disability. *Augment Altern Commun*. 2013; 29(4): 360-73. doi: 10.3109/07434618.2013.849753.
- [23] Reichle J, York J, Sigafoos J. Implementing augmentative and alternative communication: Strategies for learners with severe disabilities. Pennsylvania: Paul H. Brookes Publishing; 1991.
- [24] Fallon K, Light J, Achenbach A. The semantic organization patterns of young children: Implications for augmentative and alternative communication. *Augment Altern Commun*. 2003; 19(2): 74-85. doi: 10.1080/0743461031000112061.
- [25] Porter G. Pragmatic Organization Dynamic Display Communication Books Direct Access Templates. Cerebral Palsy Education Centre. 2008.
- [26] Dodd JL. Augmentative and alternative communication intervention: an intensive, immersive, socially based service delivery model. California: Plural Publishing; 2017.
- [27] Wilkinson KM, Jagaroo V. Contributions of principles of visual cognitive science to AAC system display design. *Augment Altern Commun*. 2004; 20(3): 123-36. doi: 10.1080/07434610410001699717.

- [28] Wolfe JM. Guided Search 2.0: A revised model of visual search. *Psychon Bull Rev.* 1994; 1: 202-38. doi: 10.3758/BF03200774.
- [29] Wolfe, J., Horowitz, T. What attributes guide the deployment of visual attention and how do they do it?. *Nat Rev Neurosci.* 2004; 5, 495-501. doi: 10.1038/nrn1411.
- [30] Munir F, Cornish KM, Wilding J. A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia.* 2000; 38(9): 1261-70. doi: 10.1016/S0028-3932(00)00036-1.
- [31] Lanfranchi S, Carretti B, Spanò G, Cornoldi C. A specific deficit in visuospatial simultaneous working memory in Down syndrome. *J Intellect Disabil Res.* 2009; 53(5): 474-83. doi: 10.1111/j.1365-2788.2009.01165.x.
- [32] Oi Y, Okuzumi H, Kokubun M. Visuospatial working memory in individuals with intellectual disabilities under simultaneous and sequential presentation. *J Spec Educ Res.* 2018; 7(1): 1-8. doi: 10.6033/specialeducation.7.1.
- [33] Bailey BR, Downing J. Using visual accents to enhance attending to communication symbols for students with severe multiple disabilities. *Review.* 1994; 26: 101-19.
- [34] Davidoff J. Cognition through color. Massachusetts: The MIT Press; 1991.
- [35] Davidoff J. The neuropsychology of color. In: Hardin CL, Maffi L. Color categories in thought and language. New York: Cambridge University Press; 1997.
- [36] Hanna A, Remington R. The representation of color and form in long-term memory. *Memory & Cognition.* 1996; 24(3): 322-30. doi: 10.3758/BF03213296.
- [37] Sperling G, Reeves A, Blaser E, Lu ZL, Weichselgartner E. Two computational models of attention. In: Braun J, Koch C, Davis J, editors. Visual attention and cortical circuits. Massachusetts: MIT Press; 2001; 177-214.
- [38] Gegenfurtner KR, Rieger J. Sensory and cognitive contributions of color to the recognition of natural scenes. *Curr Biol.* 2000; 10(13): 805-8.
- [39] Párraga CA, Troscianko T, Tolhurst D. Spatiochromatic properties of natural images and human vision. *Curr Biol.* 2002; 12(6): 483-7.
- [40] Wurm LH, Legge GE, Isenberg LM, Luebker A. Color improves object recognition in normal and low vision. *J Exp Psychol Hum Percept Perform.* 1993; 19(4): 899. doi: 10.1037/0096-1523.19.4.899.
- [41] Schulz MF, Sanocki T. Time course of perceptual grouping by color. *Psychol Sci.* 2003; 14(1): 26-30. doi: 10.1111/1467-9280.0141.
- [42] Wilkinson KM, Carlin M, Jagaroo V. Preschoolers' speed of locating a target symbol under different color conditions. *Augment Altern Commun.* 2006; 22(2): 123-33. doi: 10.1080/07434610500483620.
- [43] Wilkinson K, Carlin M, Thistle J. The role of color cues in facilitating accurate and rapid location of aided symbols by children with and without Down syndrome. *Am J Speech Lang Pathol.* 2008; 17(2): 179-93. doi: 10.1044/1058-0360(2008/018).
- [44] Thistle JJ, Wilkinson K. The effects of color cues on typically developing preschoolers' speed of locating a target line drawing: Implications for augmentative and alternative communication display design. *Am J Speech Lang Pathol.* 2009; 18(3): 231-40. doi: 10.1044/1058-0360(2009/08-0029).
- [45] Wilkinson KM, O'Neill T, McIlvane WJ. Eye-tracking measures reveal how changes in the design of aided AAC displays influence the efficiency of locating symbols by school-age children without disabilities. *J Speech Lang Hear Res.* 2014; 57(2): 455-66. doi: 10.1044/2013_JSLHR-L-12-0159.
- [46] Wilkinson KM, Madel M. Eye tracking measures reveal how changes in the design of displays for augmentative and alternative communication influence visual search in individuals with Down syndrome or autism spectrum disorder. *Am J Speech Lang Pathol.* 2019; 28(4): 1649-58. doi: 10.1044/2019_AJSLP-19-0006.
- [47] Wilkinson KM, McIlvane WJ. Perceptual factors influence visual search for meaningful symbols in individuals with intellectual disabilities and Down syndrome or autism spectrum disorders. *Am J Intellect Dev Disabil.* 2013; 118(5): 353-64. doi: 10.1352/1944-7558-118.5.353.
- [48] Hetzroni O, Ne'eman A. Influence of color on acquisition and generalization of graphic symbols. *J Intellect Disabil Res.* 2013; 57(7): 669-80. doi: 10.1111/j.1365-2788.2012.01584.x.
- [49] Wilkinson KM, Coombs B. Preliminary exploration of the effect of background color on the speed and accuracy of search for an aided symbol target by typically developing preschoolers. *Early Child Serv (San Diego).* 2010; 4(3): 171-83. PMID: 26457074.
- [50] Wilkinson KM, Snell J. Facilitating children's ability to distinguish symbols for emotions: The effects of background color cues and spatial arrangement of symbols on accuracy and speed of search. *Am J Speech Lang Pathol.* 2011; 20(4): 288-301. doi: 10.1044/1058-0360(2011/10-0065).
- [51] Wilkinson K, Weiss A. Background color cues do not facilitate attention to single symbols by individuals with Down syndrome. Poster presentation at: Annual Conference of the American Speech-Language Hearing Association (ASHA); 2017 Nov; Los Angeles, CA.
- [52] Thistle JJ, Wilkinson K. Effects of background color and symbol arrangement cues on construction of multi-symbol messages by young children without disabilities: Implications for aided AAC design. *Augment Altern Commun.* 2017; 33(3): 160-9. doi: 10.1080/07434618.2017.1336571.
- [53] Bialystok E. Factors in the growth of linguistic awareness. *Where Language Meets Thought.* New York. Routledge. 1986; 5-25.
- [54] Wilkinson KM, Gilmore R, Qian Y. Judicious arrangement of symbols on a simulated augmentative and alternative communication display optimizes visual attention by individuals with Down syndrome. *J Speech Lang Hear Res.* 2022; 65(2): 710-26. doi: 10.1044/2021_JSLHR-21-00278.

- [55] Bulakowski PF, Post RB, Whitney D. Reexamining the possible benefits of visual crowding: Dissociating crowding from ensemble percepts. *Atten Percept Psychophys.* 2011; 73(4): 1003-9. doi: 10.3758/s13414-010-0086-2.
- [56] Keshvari S, Rosenholtz R. Pooling of continuous features provides a unifying account of crowding. *J Vis.* 2016; 16(3): 1-15. doi: 10.1167/16.3.39.
- [57] Kinsbourne M. *Neuropsychology of attention.* Neuropsychology. Amsterdam: Elsevier; 1994: 105-23.
- [58] Reuter-Lorenz PA, Kinsbourne M, Moscovitch M. Hemispheric control of spatial attention. *Brain Cogn.* 1990; 12(2): 240-66.
- [59] Mesulam M-M. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci.* 1999; 354(1387): 1325-46. doi: 10.1098/rstb.1999.0482.
- [60] Kosslyn SM. Seeing and imagining in the cerebral hemispheres: A computational approach. In: *Readings in Cognitive Science: A Perspective from Psychology and Artificial Intelligence.* Amsterdam: Elsevier; 2013; 615-42. doi: 10.1016/B978-1-4832-1446-7.50052-2.
- [61] Pizzagalli D, Regard M, Lehmann D. Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport.* 1999; 10(13): 2691-8.
- [62] Sergent J, Signoret J-L. Varieties of functional deficits in prosopagnosia. *Cereb Cortex.* 1992; 2(5): 375-88. doi: 10.1093/cercor/2.5.375.



Review article: Designing grid displays in AAC systems to enhance accuracy and reduce latency in symbol searching

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ABSTRACT

Augmentative and Alternative Communication (AAC) systems support individuals with complex communication needs. This review article examines factors influencing the design of grid displays in AAC systems to enhance symbol searching accuracy and reduce latency. Four key areas are identified: the organization of symbols, color cues, visual crowding, and symbol location. Effective symbol organization, such as semantic-syntactic and schematic displays, can facilitate efficient communication, while color cues may improve visual attention and memory recall. Managing visual crowding and strategically placing symbols based on visual field biases and motor control abilities are also crucial. By optimizing these elements, speech-language pathologists can develop AAC displays that improve user communication outcomes. The findings provide guidelines for designing user-centered AAC systems tailored to individual cognitive, motor, and sensory needs.

Introduction

Augmentative and alternative communication (AAC) is a field of clinical practice that serves the demands of individuals with complex communication needs, which are defined by deficiencies in an expressive mode (e.g., speaking and writing) and/or a receptive mode of communication (e.g., spoken language comprehension). The communication competence of those individuals fails to meet their communication needs in various circumstances (e.g., communicating with unfamiliar communication partners and/or environments, noisy environments, group talking, etc.). The impairments that feasibly result in complex communication needs may include congenital disabilities (e.g., cerebral palsy, developmental apraxia of speech, etc.), acquired disabilities (e.g., amyotrophic lateral sclerosis, stroke, etc.), or neurological differences (e.g., autistic spectrum disorders, down syndrome, etc.).^{1,2}

There are two main types of AAC systems: Unaided and aided. Unaided systems involve AAC modes that do not require an external tool. These systems include gestures, vocalizations, finger spelling, manual signs, facial expressions, etc. Aided systems, on the other hand, require external tools. These systems include writing, photographs, natural objects, communication boards, etc. Aided systems also come in three forms: low-tech (i.e., nonelectronic AAC forms), such as writing, natural objects, and communication boards; mid-tech (i.e., battery-powered electronic AAC forms), such as single-button-communication switches and GoTalk³, and high-tech (i.e., electronic AAC

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forms with more advanced processors) such as Tablet-based speech-output technologies and speech generating devices.^{1,2}

There are two significant types of display layout used in picture-based AAC systems (e.g., communication boards/books, drawings (or line drawings), speech-generating devices, etc.): Visual scene display (VSD) and grid. VSD embedded vocabulary concepts within natural scenes (i.e., typically photographs) according to each AAC user's life. Vocabulary words are represented in pictures, and vocabulary words in each category are grouped in each scene.⁴⁻⁶ For example, in the kitchen scene, vocabulary words such as stove, kettle, fridge, cooking, and hungry are embedded. In contrast, the grid layout presents vocabulary words as graphic symbols arranged in rows and columns in a grid pattern. Each grid contains a single graphic symbol and is isolated in physical space.²

Different display layouts may influence the efficiency of AAC for communication. For instance, it has been reported that VSD is more uncomplicated to learning than grid layout for beginning communicators and young children.⁷⁻¹⁰ The AAC display's design should promote users' ability to communicate. Communication proficiency may include the user's motivation,^{11,12} vocabulary words corresponding to their needs and interests,² communication speed and accuracy,^{2,13-15} and other factors. To design the AAC display to support communication competence, many research studies revealed that the display should be created by the individual's cognitive/linguistic, literacy, motor, sensory, and perceptual abilities.¹⁶⁻¹⁸ Otherwise, an unsuitable AAC display design might impose additional demands on users to create messages, leading to challenges and frustration for the user and communication partners.¹⁹

The latency and accuracy of symbol searching are among the key factors significantly contributing to

AAC users' communication effectiveness. Many studies have explored the elements that impact the latency and accuracy of symbol searching. This review article intends to report and summarize the factors in designing the grid displays that enhance AAC users' latency and accuracy, providing a guideline for speech-language pathologists. According to the review, there are four primary areas of research interest related to symbol searching latency and accuracy when designing grid displays: (a) Strategies for organizing symbols, (b) Color of symbols, (c) Visual crowding, and (d) Location of symbols.

Strategies for organizing symbols

This domain concerns how symbols are arranged on a page to facilitate efficient symbol searches. Currently, there are seven types of symbol organization: (a) Semantic-syntactic, (b) Schematic, (c) Taxonomic, (d) Pragmatically organized displays, (e) Alphabetical, (f) Chronological, and (g) Idiosyncratic. Each type possesses distinct characteristics, necessitating careful decision-making to match the organization to individuals' abilities and preferences. For example, Burke, Beukelman, and Hux reported that participants with traumatic brain injury (TBI) preferred to use schematic grid displays despite showing better communication competency when using alphabetic grid displays.²⁰

A semantic-syntactic grid displays organized symbols according to syntactic functions (i.e., part of speech). Each page contains various types of words. Following Fitzgerald's Key Format, subjects, verbs, adjectives, objects, places, times, and so on are arranged from left to right, respectively.²¹ This organization is designed to promote language learning in individuals with complex communication needs.² The depiction of semantic-syntactic grid displays is shown in Figure 1.



Figure 1. Semantic-syntactic grid displays.

The symbols were sourced from ARASAAC and designed by Sergio Palao.

Schematic grid displays, also called activity grid displays, organize symbols based on activity themes such as routines, zoo visits, birthday parties, gardening, and other activities. Each page includes nouns (e.g., people, places, animals, plants), verbs, and prepositions related to the theme. An example of a schematic grid display is shown in Figure 2. Research studies suggest that schematic grid displays facilitate AAC symbol learning.^{22,23} However, there are two main disadvantages to this type of display. First, the exact vocabulary words may

repeatedly appear on different pages, leading to increased memory load in high-tech devices (e.g., smartphones and tablets) and added weight in low-tech AAC forms (e.g., communication boards). Second, this arrangement reduces the automaticity of learning using the AAC system, as users must individually learn the different locations of the target word (i.e., symbol) on each schematic page. It is recommended that schematic pages be combined with semantic-syntactic grid displays.²

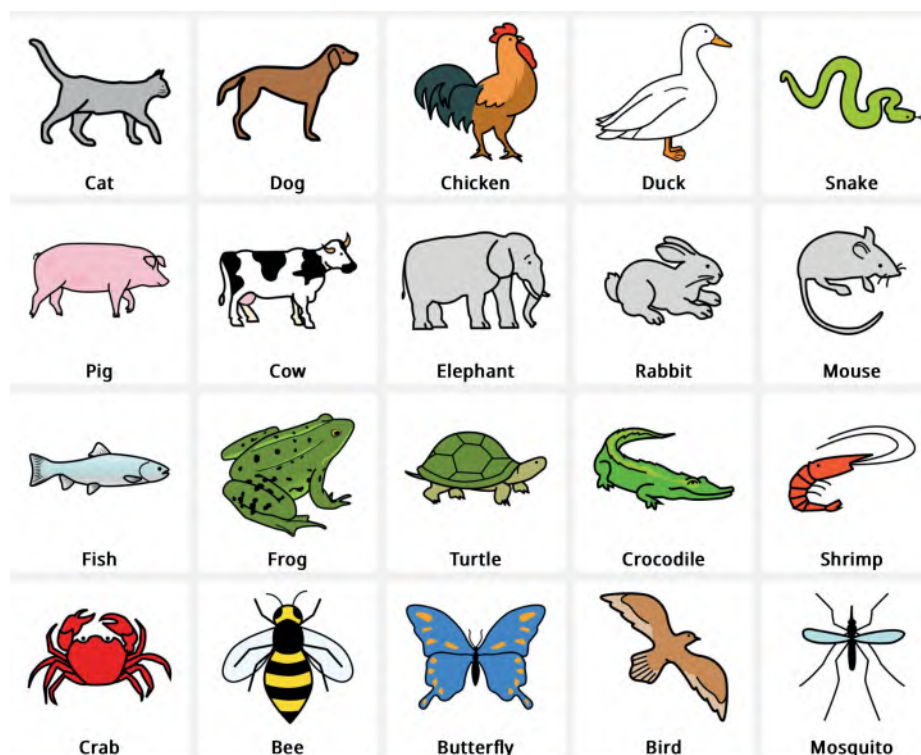


Figure 2. The schematic grid displays the animal theme.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The taxonomic grid displays symbols in categories such as fruits, animals, family members, places, clothes, action words, and so on. This type of display requires users to comprehend the concept of categorization, making it unsuitable for individuals younger than six or seven years old.²⁴ Furthermore, taxonomic grid displays have a significant drawback, as they necessitate extensive navigation between pages to find target words. Consequently, this display format may be appropriate for individuals with complex communication needs who use AAC to supplement their speech to clarify specific words rather than relying on AAC as their primary means of communication.²

Pragmatically organized displays incorporate multiple types of display organization to mitigate the limitations of each type, such as the time-consuming

nature of searching for target symbols. By integrating semantic-syntactic, taxonomic, and schematic grid displays, the time spent searching for symbols within specific conversational contexts—such as discussing a visit to the zoo—can be reduced. Examples of systems using this type of organization include Pragmatic Organization Dynamic Displays (PODD), Voco Chat, and Snap Core First, each offering unique features. For instance, PODD is the inclusion of a navigation page, which directs users to the target symbols through page tabs such as the main page (i.e., semantic-syntactic), food category (i.e., taxonomic), ordering food (i.e., schematic), conversational repair (i.e., taxonomic), and so on.²⁵ An example of PODD is illustrated in Figure 3. The primary disadvantage of this type of display is the potential for the exact words or symbols to appear repeatedly across multiple pages.²



Figure 3. Starter page of Pragmatic Organization Dynamic Displays (PODD).
The symbols were sourced from ARASAAC and designed by Sergio Palao.

An alphabetic grid displays organized symbols in alphabetical order. For instance, the first page contains words starting with “A,” and the second page includes words beginning with “B,” and so forth. This organization may be appropriate for literate individuals. Moreover, this display format might be ideal for individuals with complex communication needs who use AAC to enhance their speech by clarifying specific words rather than using AAC as their primary mode of communication.²

Chronological grid displays, also known as visual schedules or calendar systems, organize activities in sequential order, either in rows or columns. This arrangement helps individuals follow a structured sequence of tasks, reducing challenging behaviors that may arise during activity transitions. An example of a chronological grid display is Figure 4.

Idiosyncratic grid displays are personalized arrangements of symbols tailored to an individual’s unique preferences, needs, or interests that fit their cognitive organization or abilities, such as organizing by favorite movies, personal pets, etc. These displays are customized to align with the user’s communication style and requirements.²



Figure 4. Chronological grid displays related to the morning routine.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

Color of the symbols

Many cognitive factors affect how successfully AAC users employ grid display, but visual cognition is the factor that contributes most in terms of grid display.²⁶⁻²⁸ Visuospatial processing is considered the primary skill needed to use visually-based aided AAC systems.²⁶ Visuospatial processing is integral visual skills, including symbol perception (i.e., the ability to notice the presence of a symbol on a display), symbol discrimination (i.e., the ability to distinguish between two symbols on a display), identification (i.e., the ability to recognize what a symbol represents), and recall (i.e., ability to remember where the symbol is located on display).^{26,27} Individuals with developmental and intellectual disabilities frequently experience difficulty inhibiting their attention to distracting stimuli.^{29,30} This challenge may be related to issues about visuospatial processing, especially visuospatial working memory.^{30,31} To reduce this issue, researchers examine the effects of color cues on symbol learning in children with and without disabilities.

Research has shown that the use of color can have a positive impact on processing and aiding the learning of symbol meaning for children with multiple disabilities.^{26,32-34} These findings were supported by evidence that color facilitates image retrieval.^{26,35,36} Visual short-term memory may be improved when distinct colors represent different features of an object.³⁷ Long-term visual memory is strengthened when specific colors and forms are associated with memory representation.³⁵ In addition, Párraga *et al.* indicated that color can influence attention and enhance perception speed.³⁸ Therefore, numerous studies have investigated the impact of color on attention and the speed of target symbol searching, focusing on two primary aspects: the internal symbol color and the symbol

background color.

Internal symbol color attracts attention, differentiates between similar objects, and facilitates object recognition.³⁹ Moreover, surface color can aid in the grouping of objects.⁴⁰ According to these findings, many researchers intended to investigate whether the internal symbol color could increase the speed and accuracy of locating the symbol in grid displays when the like-colored symbols were grouped. Most research outcomes showed that grouping symbols with similar colors improves the efficiency of finding the symbol in the array.⁴¹⁻⁴⁵ This might be because clustering like-colored symbols decreases cognitive load and enhances visual attention.^{41,42,44,46}

For example, Wilkinson and Madel measured the gaze pattern of six children with Down syndrome and six children with autism by using eye-tracking technology. The results demonstrated that participants significantly focused on target symbols while fixating less on distractors when the like-colored symbols were clustered together. An example of internal color cues with a clustering arrangement is illustrated in Figure 5. Nevertheless, Hetzroni and Ne'eman's research findings indicated that all four preschoolers with autism showed no differences in success in learning recognition of the new vocabulary, regardless of the level of color (i.e., grey-scale symbols versus color symbols) included in the symbols.⁴⁷ Although clustering symbols on the array that shared internal color could improve symbol searching accuracy and reduce latency, there was a notable limitation. The number of symbols that do not share the same internal color makes it impossible to arrange them by clustering based on internal color. Consequently, some researchers explored the effects of background color cues on the accuracy and latency of the symbol-searching process.

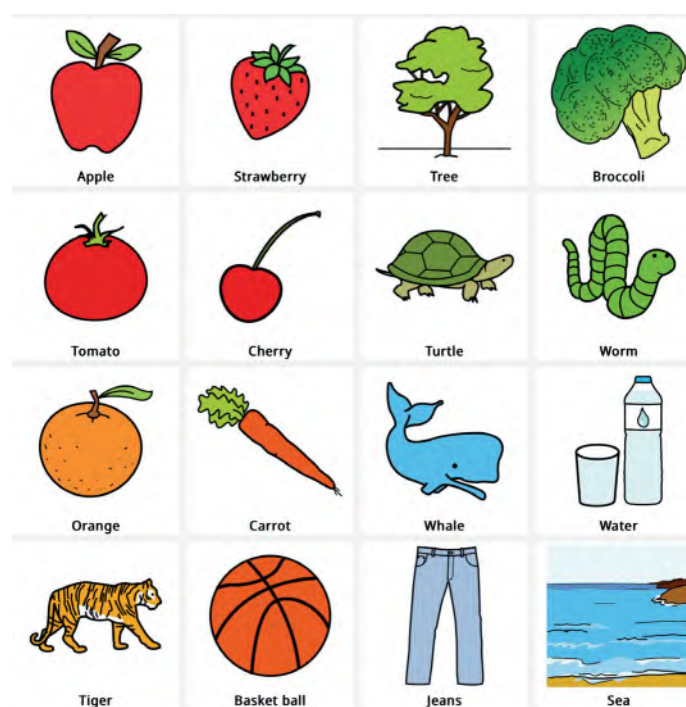


Figure 5. Internal color cues with a clustering arrangement.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The influence of symbol background color was examined concerning two primary effects: (a) the speed of identifying individual symbols functioning as a semantic cue, and (b) the speed of identifying a sequence of symbols (i.e., for constructing multi-symbol messages) functioning as a syntactic cue. Most research studies have shown that background color cues do not improve the speed or accuracy of single symbol searching in children with typical development^{43,48,49} or Down syndrome.⁵⁰ For example, Wilkinson and Snell investigated whether background color cueing helps children with typical development identify emotion symbols grouped by valence. The results indicated that background color did not enhance the children's ability to identify symbols more quickly.⁴⁹ These studies reported that background color cues related to semantics neither provided any advantage in searching nor slowed down the process of locating a single symbol due to the distracting effect. However, One study demonstrated that symbol background color increased the speed of single symbol searching in adults without disabilities and recommended using background color cues with communication partners to assist individuals who rely on AAC in locating target symbols on a grid display.⁵¹

Likewise, in terms of using background colors as a syntactic cue (e.g., word-class categories such as red background for pronouns, blue background for action verbs, yellow background for adverbs, etc.), studies reported that background color cues did not aid multi-symbol message construction in young children. This might be because background color cueing as a syntactic cue might be linked to metalinguistic skills, typically emerging between 5 and 7 years of age.⁵² Therefore, employing background color cueing to enhance sentence construction may only benefit older individuals with intact metalinguistic awareness.⁵¹ However, Wilkinson et al. reported that background color cueing reduced the latency in locating the target symbol. This may be attributed to the fact that the participants in the study were adults with Down syndrome, whose average receptive vocabulary age was approximately 7 years and 0 months.⁵³ The illustration of using background-color cueing as a syntactic cue is shown in Figure 1.

The impact of background color cues remains a subject of ongoing research. The researchers suggest that the lack of benefit from background color cues in young children may be due to the increased cognitive load imposed by the need to interpret the color cues, a skill that young children may not yet possess.⁴⁹ This aligns with Wilkinson and Jagaroo's assertion that the effectiveness of color cues depends on the user's cognitive abilities and the complexity of the visual display.²⁶

Visual crowding

Visual crowding or clutter refers to a phenomenon where symbols become indistinguishable due to proximity. In a standard grid display, multiple rows and columns of symbols are arranged adjacently, without intervening space, and with uniform dimensions. This configuration leads to difficulties in distinguishing individual elements, limits eye and hand movement, and impedes visual

search efficiency.^{19,54} The recognition of an object is hindered when the spacing between objects is too narrow, particularly for objects that are not centrally located.⁵⁵ Wilkinson et al. conducted a study to evaluate the impact of visual crowding across four different arrangement conditions (i.e., closed-set grid, widely spaced grid, perimeter, and corners) on latency and fixation to distractors. In each arrangement, symbols were grouped according to grammatical categories, including subjects, actions, objects, and descriptors. The results indicated that participants with Down syndrome were less likely to fixate on irrelevant symbols when the symbols were more widely spaced. However, reducing visual crowding did not lead to an improvement in the latency of symbol searching.⁵³

Location of symbols

According to research studies, symbol location is influenced by two key aspects: visual field biases and motor control ability. Visual field biases can impact visual-spatial performance, leading individuals to attend to one-half of the visual field preferentially.^{56,57} For instance, individuals with left-hemisphere dominance often focus more on the right visual field.⁵⁸ Moreover, research indicates that symbols with abstract forms are best positioned on the right side of the display,⁵⁹ whereas symbols depicting emotional facial expressions and geometric configurations are more effectively placed on the left side.^{60,61}

Furthermore, an individual's motor control ability must be assessed to position symbols optimally, ensuring easier access. Beukelman and Light provided an example where frequently used symbols are placed on the side of the display that corresponds to the hand with better motor control.²

Conclusion

The effectiveness of communication for AAC users is significantly influenced by the latency and accuracy of symbol searching. This review article has summarized vital factors that contribute to these aspects, focusing on the design of grid displays that enhance symbol searching efficiency. The primary areas of interest include the organization of symbols, the use of color, visual crowding, and the location of symbols on the grid. By understanding and applying these factors, speech-language pathologists can create more effective AAC systems that improve user communication outcomes. The research highlights the importance of strategic symbol arrangement, appropriate color cues, managing visual crowding, and considering individual visual and motor control abilities in designing grid displays. These insights provide a valuable guideline for optimizing AAC tools to better support users with complex communication needs.

References

- [1] Association AS-L-H. Augmentative and alternative communication (AAC) [cited 2024 July 20]. Available from: <https://www.asha.org/practice-portal/professional-issues/augmentative-and-alternative-communication/>.

- [2] Beukelman D, Light J. Augmentative and alternative communication: Supporting children and adults with complex communication needs. 5th Ed. Pennsylvania: Paul H. Brookes Publishing; 2020.
- [3] Desch LW, Gaebler-Spira D, Council on children with disabilities. Prescribing assistive-technology systems: Focus on children with impaired communication. *Pediatrics*. 2008; 121(6): 1271-80. doi:10.1542/peds.2008-0695.
- [4] Blackstone S, Light J, Beukelman D, Shane H. Visual scene displays. *Augment Comm News*. 2004; 16(2): 1-6.
- [5] Wilkinson KM, Light J. Preliminary investigation of visual attention to human figures in photographs: Potential considerations for the design of aided AAC visual scene displays. *J Speech Lang Hear Res*. 2011; 54(6): 1644-57. doi:10.1044/1092-4388(2011/10-0098).
- [6] Dietz A, McKelvey M, Beukelman DR. Visual scene displays (VSD): New AAC interfaces for persons with aphasia. *Perspect Augment Altern Commun*. 2006; 15(1): 13-7. doi: 10.1044/aac15.1.13.
- [7] Drager KD, Light JC, Speltz JC, Fallon KA, Jeffries LZ. The performance of typically developing 2½-year-olds on dynamic display AAC technologies with different system layouts and language organizations. *J Speech Lang Hear Res*. 2003; 46(2): 298-312. doi: 10.1044/1092-4388(2003/024).
- [8] Drager KD, Light JC, Carlson R, D'Silva K, Larsson B, Pitkin L, Stopper G. Learning of dynamic display AAC technologies by typically developing 3-year-olds. *J Speech Lang Hear Res*. 2004; 47(5): 1133-48. doi: 10.1044/1092-4388(2004/084).
- [9] Drager KD, Light J, Currall J, Muttiah N, Smith V, Kreis D, Nilam-Hall A, Parratt D, Schuessler K, Shermetta K, Wiscount J. AAC technologies with visual scene displays and "just in time" programming and symbolic communication turns expressed by students with severe disability. *J Intellect Dev Disabil*. 2019; 44(3): 321-36. doi: 10.3109/13668250.2017.1326585.
- [10] Holyfield C, Caron JG, Drager K, Light J. Effect of mobile technology featuring visual scene displays and just-in-time programming on communication turns by preadolescent and adolescent beginning communicators. *Int J Speech Lang Pathol*. 2019; 21(2): 201-11. doi: 10.1080/17549507.2018.1441440.
- [11] Higginbotham DJ, Shane H, Russell S, Caves K. Access to AAC: Present, past, and future. *Augment Altern Commun*. 2007; 23(3): 243-57. doi: 10.1080/07434610701571058.
- [12] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Positioning students with cerebral palsy to use augmentative and alternative communication. *Lang Speech Hear Serv Sch*. 1990; 21(1): 15-21. doi: 10.1044/0161-1461.2101.15.
- [13] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Hierarchy of conversational rule violations involving utterance-based augmentative and alternative communication systems. *Augment Altern Commun*. 2008; 24(2): 149-61. doi: 10.1080/07434610802038288
- [14] McCoy KF, Bedrosian JL, Hoag LA, Johnson DE. Brevity and speed of message delivery trade-offs in augmentative and alternative communication. *Augment Altern Commun*. 2007; 23(1): 76-88. doi: 10.1080/07434610600924515.
- [15] Todman J. Rate and quality of conversations using a text-storage AAC system: Single-case training study. *Augment Altern Commun*. 2000; 16(3): 164-79. doi: 10.1080/07434610012331279024.
- [16] Blackstone S. Designing displays: Hints and examples. *Augment Comm News*. 1993; 6(1): 1-6.
- [17] Light J, Lindsay P. Cognitive science and augmentative and alternative communication. *Augment Altern Commun*. 1991; 7(3): 186-203. doi: 10.1080/07434619112331275893.
- [18] Johnson JM, Inglebret E, Jones C, Ray J. Perspectives of speech language pathologists regarding success versus abandonment of AAC. *Augment Altern Commun*. 2006; 22(2): 85-99. doi: 10.1080/07434610500483588.
- [19] Light J, Wilkinson KM, Thiessen A, Beukelman DR, Fager SK. Designing effective AAC displays for individuals with developmental or acquired disabilities: State of the science and future research directions. *Augment Altern Commun*. 2019; 35(1): 42-55. doi: 10.1080/07434618.2018.1558283
- [20] Burke R, Beukelman DR, Hux K. Accuracy, efficiency and preferences of survivors of traumatic brain injury when using three organization strategies to retrieve words. *Brain Inj*. 2004; 18(5): 497-507. doi: 10.1080/02699050310001645784.
- [21] Fitzgerald E, editor. Straight language for the deaf. In: *Proceedings of the Twenty-Eighth Meeting of the Convention of American Instructors of the Deaf*; 1933; West Trenton, New Jersey.
- [22] Dada S, Huguet A, Bornman J. The iconicity of picture communication symbols for children with English additional language and mild intellectual disability. *Augment Altern Commun*. 2013; 29(4): 360-73. doi: 10.3109/07434618.2013.849753.
- [23] Reichle J, York J, Sigafoos J. Implementing augmentative and alternative communication: Strategies for learners with severe disabilities. Pennsylvania: Paul H. Brookes Publishing; 1991.
- [24] Fallon K, Light J, Achenbach A. The semantic organization patterns of young children: Implications for augmentative and alternative communication. *Augment Altern Commun*. 2003; 19(2): 74-85. doi: 10.1080/0743461031000112061.
- [25] Porter G. Pragmatic Organization Dynamic Display Communication Books Direct Access Templates. Cerebral Palsy Education Centre. 2008.
- [26] Dodd JL. Augmentative and alternative communication intervention: an intensive, immersive, socially based service delivery model. California: Plural Publishing; 2017.
- [27] Wilkinson KM, Jagaroo V. Contributions of principles of visual cognitive science to AAC system display design. *Augment Altern Commun*. 2004; 20(3): 123-36. doi: 10.1080/07434610410001699717.

- [28] Wolfe JM. Guided Search 2.0: A revised model of visual search. *Psychon Bull Rev.* 1994; 1: 202-38. doi: 10.3758/BF03200774.
- [29] Wolfe, J., Horowitz, T. What attributes guide the deployment of visual attention and how do they do it?. *Nat Rev Neurosci.* 2004; 5, 495-501. doi: 10.1038/nrn1411.
- [30] Munir F, Cornish KM, Wilding J. A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia.* 2000; 38(9): 1261-70. doi: 10.1016/S0028-3932(00)00036-1.
- [31] Lanfranchi S, Carretti B, Spanò G, Cornoldi C. A specific deficit in visuospatial simultaneous working memory in Down syndrome. *J Intellect Disabil Res.* 2009; 53(5): 474-83. doi: 10.1111/j.1365-2788.2009.01165.x.
- [32] Oi Y, Okuzumi H, Kokubun M. Visuospatial working memory in individuals with intellectual disabilities under simultaneous and sequential presentation. *J Spec Educ Res.* 2018; 7(1): 1-8. doi: 10.6033/spededucation.7.1.
- [33] Bailey BR, Downing J. Using visual accents to enhance attending to communication symbols for students with severe multiple disabilities. *Review.* 1994; 26: 101-19.
- [34] Davidoff J. Cognition through color. Massachusetts: The MIT Press; 1991.
- [35] Davidoff J. The neuropsychology of color. In: Hardin CL, Maffi L. Color categories in thought and language. New York: Cambridge University Press; 1997.
- [36] Hanna A, Remington R. The representation of color and form in long-term memory. *Memory & Cognition.* 1996; 24(3): 322-30. doi: 10.3758/BF03213296.
- [37] Sperling G, Reeves A, Blaser E, Lu ZL, Weichselgartner E. Two computational models of attention. In: Braun J, Koch C, Davis J, editors. Visual attention and cortical circuits. Massachusetts: MIT Press; 2001; 177-214.
- [38] Gegenfurtner KR, Rieger J. Sensory and cognitive contributions of color to the recognition of natural scenes. *Curr Biol.* 2000; 10(13): 805-8.
- [39] Párraga CA, Troscianko T, Tolhurst D. Spatiochromatic properties of natural images and human vision. *Curr Biol.* 2002; 12(6): 483-7.
- [40] Wurm LH, Legge GE, Isenberg LM, Luebker A. Color improves object recognition in normal and low vision. *J Exp Psychol Hum Percept Perform.* 1993; 19(4): 899. doi: 10.1037/0096-1523.19.4.899.
- [41] Schulz MF, Sanocki T. Time course of perceptual grouping by color. *Psychol Sci.* 2003; 14(1): 26-30. doi: 10.1111/1467-9280.0141.
- [42] Wilkinson KM, Carlin M, Jagaroo V. Preschoolers' speed of locating a target symbol under different color conditions. *Augment Altern Commun.* 2006; 22(2): 123-33. doi: 10.1080/07434610500483620.
- [43] Wilkinson K, Carlin M, Thistle J. The role of color cues in facilitating accurate and rapid location of aided symbols by children with and without Down syndrome. *Am J Speech Lang Pathol.* 2008; 17(2): 179-93. doi: 10.1044/1058-0360(2008/018).
- [44] Thistle JJ, Wilkinson K. The effects of color cues on typically developing preschoolers' speed of locating a target line drawing: Implications for augmentative and alternative communication display design. *Am J Speech Lang Pathol.* 2009; 18(3): 231-40. doi: 10.1044/1058-0360(2009/08-0029).
- [45] Wilkinson KM, O'Neill T, McIlvane WJ. Eye-tracking measures reveal how changes in the design of aided AAC displays influence the efficiency of locating symbols by school-age children without disabilities. *J Speech Lang Hear Res.* 2014; 57(2): 455-66. doi: 10.1044/2013_JSLHR-L-12-0159.
- [46] Wilkinson KM, Madel M. Eye tracking measures reveal how changes in the design of displays for augmentative and alternative communication influence visual search in individuals with Down syndrome or autism spectrum disorder. *Am J Speech Lang Pathol.* 2019; 28(4): 1649-58. doi: 10.1044/2019_AJSLP-19-0006.
- [47] Wilkinson KM, McIlvane WJ. Perceptual factors influence visual search for meaningful symbols in individuals with intellectual disabilities and Down syndrome or autism spectrum disorders. *Am J Intellect Dev Disabil.* 2013; 118(5): 353-64. doi: 10.1352/1944-7558-118.5.353.
- [48] Hetzroni O, Ne'eman A. Influence of color on acquisition and generalization of graphic symbols. *J Intellect Disabil Res.* 2013; 57(7): 669-80. doi: 10.1111/j.1365-2788.2012.01584.x.
- [49] Wilkinson KM, Coombs B. Preliminary exploration of the effect of background color on the speed and accuracy of search for an aided symbol target by typically developing preschoolers. *Early Child Serv (San Diego).* 2010; 4(3): 171-83. PMID: 26457074.
- [50] Wilkinson KM, Snell J. Facilitating children's ability to distinguish symbols for emotions: The effects of background color cues and spatial arrangement of symbols on accuracy and speed of search. *Am J Speech Lang Pathol.* 2011; 20(4): 288-301. doi: 10.1044/1058-0360(2011/10-0065).
- [51] Wilkinson K, Weiss A. Background color cues do not facilitate attention to single symbols by individuals with Down syndrome. Poster presentation at: Annual Conference of the American Speech-Language Hearing Association (ASHA); 2017 Nov; Los Angeles, CA.
- [52] Thistle JJ, Wilkinson K. Effects of background color and symbol arrangement cues on construction of multi-symbol messages by young children without disabilities: Implications for aided AAC design. *Augment Altern Commun.* 2017; 33(3): 160-9. doi: 10.1080/07434618.2017.1336571.
- [53] Bialystok E. Factors in the growth of linguistic awareness. *Where Language Meets Thought.* New York. Routledge. 1986; 5-25.
- [54] Wilkinson KM, Gilmore R, Qian Y. Judicious arrangement of symbols on a simulated augmentative and alternative communication display optimizes visual attention by individuals with Down syndrome. *J Speech Lang Hear Res.* 2022; 65(2): 710-26. doi: 10.1044/2021_JSLHR-21-00278.

- [55] Bulakowski PF, Post RB, Whitney D. Reexamining the possible benefits of visual crowding: Dissociating crowding from ensemble percepts. *Atten Percept Psychophys.* 2011; 73(4): 1003-9. doi: 10.3758/s13414-010-0086-2.
- [56] Keshvari S, Rosenholtz R. Pooling of continuous features provides a unifying account of crowding. *J Vis.* 2016; 16(3): 1-15. doi: 10.1167/16.3.39.
- [57] Kinsbourne M. *Neuropsychology of attention.* Neuropsychology. Amsterdam: Elsevier; 1994: 105-23.
- [58] Reuter-Lorenz PA, Kinsbourne M, Moscovitch M. Hemispheric control of spatial attention. *Brain Cogn.* 1990; 12(2): 240-66.
- [59] Mesulam M-M. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci.* 1999; 354(1387): 1325-46. doi: 10.1098/rstb.1999.0482.
- [60] Kosslyn SM. Seeing and imagining in the cerebral hemispheres: A computational approach. In: *Readings in Cognitive Science: A Perspective from Psychology and Artificial Intelligence.* Amsterdam: Elsevier; 2013; 615-42. doi: 10.1016/B978-1-4832-1446-7.50052-2.
- [61] Pizzagalli D, Regard M, Lehmann D. Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport.* 1999; 10(13): 2691-8.
- [62] Sergent J, Signoret J-L. Varieties of functional deficits in prosopagnosia. *Cereb Cortex.* 1992; 2(5): 375-88. doi: 10.1093/cercor/2.5.375.



Review article: Designing grid displays in AAC systems to enhance accuracy and reduce latency in symbol searching

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ABSTRACT

Augmentative and Alternative Communication (AAC) systems support individuals with complex communication needs. This review article examines factors influencing the design of grid displays in AAC systems to enhance symbol searching accuracy and reduce latency. Four key areas are identified: the organization of symbols, color cues, visual crowding, and symbol location. Effective symbol organization, such as semantic-syntactic and schematic displays, can facilitate efficient communication, while color cues may improve visual attention and memory recall. Managing visual crowding and strategically placing symbols based on visual field biases and motor control abilities are also crucial. By optimizing these elements, speech-language pathologists can develop AAC displays that improve user communication outcomes. The findings provide guidelines for designing user-centered AAC systems tailored to individual cognitive, motor, and sensory needs.

Introduction

Augmentative and alternative communication (AAC) is a field of clinical practice that serves the demands of individuals with complex communication needs, which are defined by deficiencies in an expressive mode (e.g., speaking and writing) and/or a receptive mode of communication (e.g., spoken language comprehension). The communication competence of those individuals fails to meet their communication needs in various circumstances (e.g., communicating with unfamiliar communication partners and/or environments, noisy environments, group talking, etc.). The impairments that feasibly result in complex communication needs may include congenital disabilities (e.g., cerebral palsy, developmental apraxia of speech, etc.), acquired disabilities (e.g., amyotrophic lateral sclerosis, stroke, etc.), or neurological differences (e.g., autistic spectrum disorders, down syndrome, etc.).^{1,2}

There are two main types of AAC systems: Unaided and aided. Unaided systems involve AAC modes that do not require an external tool. These systems include gestures, vocalizations, finger spelling, manual signs, facial expressions, etc. Aided systems, on the other hand, require external tools. These systems include writing, photographs, natural objects, communication boards, etc. Aided systems also come in three forms: low-tech (i.e., nonelectronic AAC forms), such as writing, natural objects, and communication boards; mid-tech (i.e., battery-powered electronic AAC forms), such as single-button-communication switches and GoTalk³, and high-tech (i.e., electronic AAC

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forms with more advanced processors) such as Tablet-based speech-output technologies and speech generating devices.^{1,2}

There are two significant types of display layout used in picture-based AAC systems (e.g., communication boards/books, drawings (or line drawings), speech-generating devices, etc.): Visual scene display (VSD) and grid. VSD embedded vocabulary concepts within natural scenes (i.e., typically photographs) according to each AAC user's life. Vocabulary words are represented in pictures, and vocabulary words in each category are grouped in each scene.⁴⁻⁶ For example, in the kitchen scene, vocabulary words such as stove, kettle, fridge, cooking, and hungry are embedded. In contrast, the grid layout presents vocabulary words as graphic symbols arranged in rows and columns in a grid pattern. Each grid contains a single graphic symbol and is isolated in physical space.²

Different display layouts may influence the efficiency of AAC for communication. For instance, it has been reported that VSD is more uncomplicated to learning than grid layout for beginning communicators and young children.⁷⁻¹⁰ The AAC display's design should promote users' ability to communicate. Communication proficiency may include the user's motivation,^{11,12} vocabulary words corresponding to their needs and interests,² communication speed and accuracy,^{2,13-15} and other factors. To design the AAC display to support communication competence, many research studies revealed that the display should be created by the individual's cognitive/linguistic, literacy, motor, sensory, and perceptual abilities.¹⁶⁻¹⁸ Otherwise, an unsuitable AAC display design might impose additional demands on users to create messages, leading to challenges and frustration for the user and communication partners.¹⁹

The latency and accuracy of symbol searching are among the key factors significantly contributing to

AAC users' communication effectiveness. Many studies have explored the elements that impact the latency and accuracy of symbol searching. This review article intends to report and summarize the factors in designing the grid displays that enhance AAC users' latency and accuracy, providing a guideline for speech-language pathologists. According to the review, there are four primary areas of research interest related to symbol searching latency and accuracy when designing grid displays: (a) Strategies for organizing symbols, (b) Color of symbols, (c) Visual crowding, and (d) Location of symbols.

Strategies for organizing symbols

This domain concerns how symbols are arranged on a page to facilitate efficient symbol searches. Currently, there are seven types of symbol organization: (a) Semantic-syntactic, (b) Schematic, (c) Taxonomic, (d) Pragmatically organized displays, (e) Alphabetical, (f) Chronological, and (g) Idiosyncratic. Each type possesses distinct characteristics, necessitating careful decision-making to match the organization to individuals' abilities and preferences. For example, Burke, Beukelman, and Hux reported that participants with traumatic brain injury (TBI) preferred to use schematic grid displays despite showing better communication competency when using alphabetic grid displays.²⁰

A semantic-syntactic grid displays organized symbols according to syntactic functions (i.e., part of speech). Each page contains various types of words. Following Fitzgerald's Key Format, subjects, verbs, adjectives, objects, places, times, and so on are arranged from left to right, respectively.²¹ This organization is designed to promote language learning in individuals with complex communication needs.² The depiction of semantic-syntactic grid displays is shown in Figure 1.



Figure 1. Semantic-syntactic grid displays.

The symbols were sourced from ARASAAC and designed by Sergio Palao.

Schematic grid displays, also called activity grid displays, organize symbols based on activity themes such as routines, zoo visits, birthday parties, gardening, and other activities. Each page includes nouns (e.g., people, places, animals, plants), verbs, and prepositions related to the theme. An example of a schematic grid display is shown in Figure 2. Research studies suggest that schematic grid displays facilitate AAC symbol learning.^{22,23} However, there are two main disadvantages to this type of display. First, the exact vocabulary words may

repeatedly appear on different pages, leading to increased memory load in high-tech devices (e.g., smartphones and tablets) and added weight in low-tech AAC forms (e.g., communication boards). Second, this arrangement reduces the automaticity of learning using the AAC system, as users must individually learn the different locations of the target word (i.e., symbol) on each schematic page. It is recommended that schematic pages be combined with semantic-syntactic grid displays.²

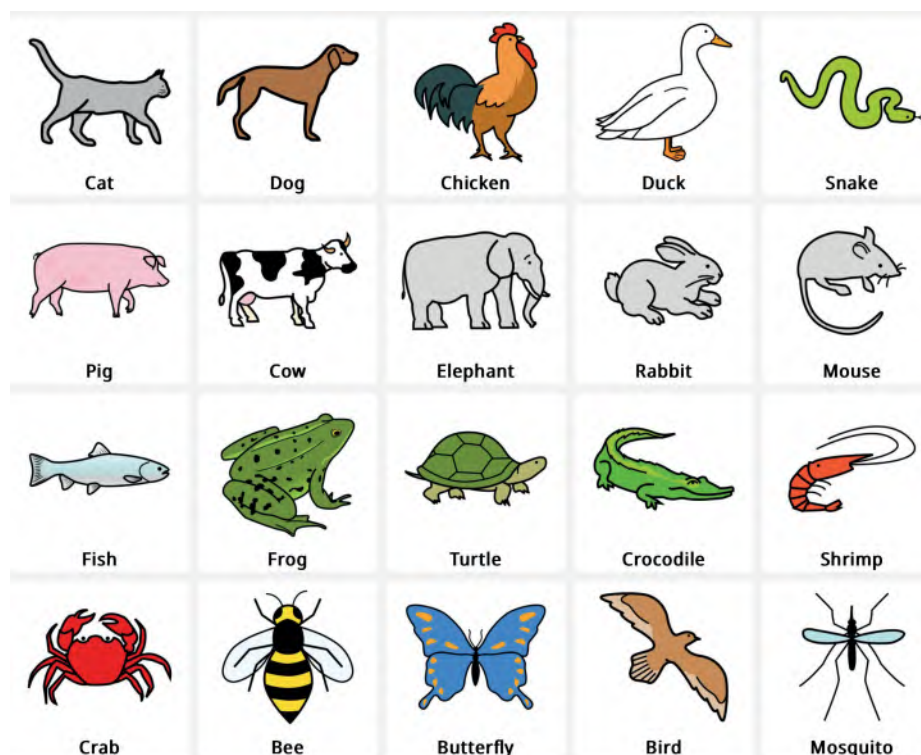


Figure 2. The schematic grid displays the animal theme.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The taxonomic grid displays symbols in categories such as fruits, animals, family members, places, clothes, action words, and so on. This type of display requires users to comprehend the concept of categorization, making it unsuitable for individuals younger than six or seven years old.²⁴ Furthermore, taxonomic grid displays have a significant drawback, as they necessitate extensive navigation between pages to find target words. Consequently, this display format may be appropriate for individuals with complex communication needs who use AAC to supplement their speech to clarify specific words rather than relying on AAC as their primary means of communication.²

Pragmatically organized displays incorporate multiple types of display organization to mitigate the limitations of each type, such as the time-consuming

nature of searching for target symbols. By integrating semantic-syntactic, taxonomic, and schematic grid displays, the time spent searching for symbols within specific conversational contexts—such as discussing a visit to the zoo—can be reduced. Examples of systems using this type of organization include Pragmatic Organization Dynamic Displays (PODD), Voco Chat, and Snap Core First, each offering unique features. For instance, PODD is the inclusion of a navigation page, which directs users to the target symbols through page tabs such as the main page (i.e., semantic-syntactic), food category (i.e., taxonomic), ordering food (i.e., schematic), conversational repair (i.e., taxonomic), and so on.²⁵ An example of PODD is illustrated in Figure 3. The primary disadvantage of this type of display is the potential for the exact words or symbols to appear repeatedly across multiple pages.²



Figure 3. Starter page of Pragmatic Organization Dynamic Displays (PODD).
The symbols were sourced from ARASAAC and designed by Sergio Palao.

An alphabetic grid displays organized symbols in alphabetical order. For instance, the first page contains words starting with “A,” and the second page includes words beginning with “B,” and so forth. This organization may be appropriate for literate individuals. Moreover, this display format might be ideal for individuals with complex communication needs who use AAC to enhance their speech by clarifying specific words rather than using AAC as their primary mode of communication.²

Chronological grid displays, also known as visual schedules or calendar systems, organize activities in sequential order, either in rows or columns. This arrangement helps individuals follow a structured sequence of tasks, reducing challenging behaviors that may arise during activity transitions.^{2,26} An example of a chronological grid display is Figure 4.

Idiosyncratic grid displays are personalized arrangements of symbols tailored to an individual’s unique preferences, needs, or interests that fit their cognitive organization or abilities, such as organizing by favorite movies, personal pets, etc. These displays are customized to align with the user’s communication style and requirements.²



Figure 4. Chronological grid displays related to the morning routine.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

Color of the symbols

Many cognitive factors affect how successfully AAC users employ grid display, but visual cognition is the factor that contributes most in terms of grid display.²⁷⁻²⁹ Visuospatial processing is considered the primary skill needed to use visually-based aided AAC systems.²⁷ Visuospatial processing is integral visual skills, including symbol perception (i.e., the ability to notice the presence of a symbol on a display), symbol discrimination (i.e., the ability to distinguish between two symbols on a display), identification (i.e., the ability to recognize what a symbol represents), and recall (i.e., ability to remember where the symbol is located on display).^{27,28} Individuals with developmental and intellectual disabilities frequently experience difficulty inhibiting their attention to distracting stimuli.^{30,31} This challenge may be related to issues about visuospatial processing, especially visuospatial working memory.^{31,32} To reduce this issue, researchers examine the effects of color cues on symbol learning in children with and without disabilities.

Research has shown that the use of color can have a positive impact on processing and aiding the learning of symbol meaning for children with multiple disabilities.^{27,33-35} These findings were supported by evidence that color facilitates image retrieval.^{27,36,37} Visual short-term memory may be improved when distinct colors represent different features of an object.³⁸ Long-term visual memory is strengthened when specific colors and forms are associated with memory representation.³⁶ In addition, Párraga *et al.* indicated that color can influence attention and enhance perception speed.³⁹ Therefore, numerous studies have investigated the impact of color on attention and the speed of target symbol searching, focusing on two primary aspects: the internal symbol color and the symbol

background color.

Internal symbol color attracts attention, differentiates between similar objects, and facilitates object recognition.⁴⁰ Moreover, surface color can aid in the grouping of objects.⁴¹ According to these findings, many researchers intended to investigate whether the internal symbol color could increase the speed and accuracy of locating the symbol in grid displays when the like-colored symbols were grouped. Most research outcomes showed that grouping symbols with similar colors improves the efficiency of finding the symbol in the array.⁴²⁻⁴⁶ This might be because clustering like-colored symbols decreases cognitive load and enhances visual attention.^{42,43,45,47}

For example, Wilkinson and Madel measured the gaze pattern of six children with Down syndrome and six children with autism by using eye-tracking technology. The results demonstrated that participants significantly focused on target symbols while fixating less on distractors when the like-colored symbols were clustered together. An example of internal color cues with a clustering arrangement is illustrated in Figure 5. Nevertheless, Hetzroni and Ne'eman's research findings indicated that all four preschoolers with autism showed no differences in success in learning recognition of the new vocabulary, regardless of the level of color (i.e., grey-scale symbols versus color symbols) included in the symbols.⁴⁸ Although clustering symbols on the array that shared internal color could improve symbol searching accuracy and reduce latency, there was a notable limitation. The number of symbols that do not share the same internal color makes it impossible to arrange them by clustering based on internal color. Consequently, some researchers explored the effects of background color cues on the accuracy and latency of the symbol-searching process.

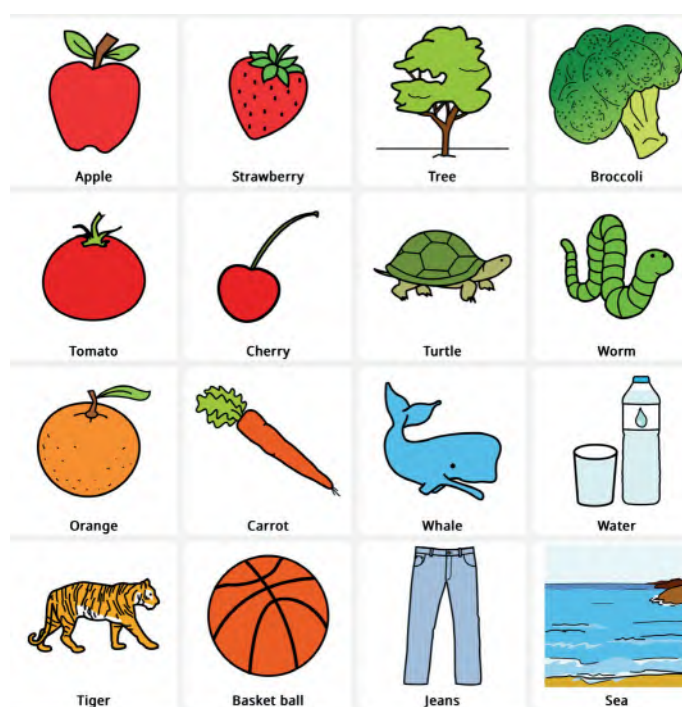


Figure 5. Internal color cues with a clustering arrangement.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The influence of symbol background color was examined concerning two primary effects: (a) the speed of identifying individual symbols functioning as a semantic cue, and (b) the speed of identifying a sequence of symbols (i.e., for constructing multi-symbol messages) functioning as a syntactic cue. Most research studies have shown that background color cues do not improve the speed or accuracy of single symbol searching in children with typical development^{44,49,50} or Down syndrome.⁵¹ For example, Wilkinson and Snell investigated whether background color cueing helps children with typical development identify emotion symbols grouped by valence. The results indicated that background color did not enhance the children's ability to identify symbols more quickly.⁵⁰ These studies reported that background color cues related to semantics neither provided any advantage in searching nor slowed down the process of locating a single symbol due to the distracting effect. However, One study demonstrated that symbol background color increased the speed of single symbol searching in adults without disabilities and recommended using background color cues with communication partners to assist individuals who rely on AAC in locating target symbols on a grid display.⁵²

Likewise, in terms of using background colors as a syntactic cue (e.g., word-class categories such as red background for pronouns, blue background for action verbs, yellow background for adverbs, etc.), studies reported that background color cues did not aid multi-symbol message construction in young children. This might be because background color cueing as a syntactic cue might be linked to metalinguistic skills, typically emerging between 5 and 7 years of age.⁵³ Therefore, employing background color cueing to enhance sentence construction may only benefit older individuals with intact metalinguistic awareness.⁵¹ However, Wilkinson *et al.* reported that background color cueing reduced the latency in locating the target symbol. This may be attributed to the fact that the participants in the study were adults with Down syndrome, whose average receptive vocabulary age was approximately 7 years and 0 months.⁵⁴ The illustration of using background-color cueing as a syntactic cue is shown in Figure 1.

The impact of background color cues remains a subject of ongoing research. The researchers suggest that the lack of benefit from background color cues in young children may be due to the increased cognitive load imposed by the need to interpret the color cues, a skill that young children may not yet possess.⁵⁰ This aligns with Wilkinson and Jagaroo's assertion that the effectiveness of color cues depends on the user's cognitive abilities and the complexity of the visual display.²⁷

Visual crowding

Visual crowding or clutter refers to a phenomenon where symbols become indistinguishable due to proximity. In a standard grid display, multiple rows and columns of symbols are arranged adjacently, without intervening space, and with uniform dimensions. This configuration leads to difficulties in distinguishing individual elements, limits eye and hand movement, and impedes visual

search efficiency.^{19,55} The recognition of an object is hindered when the spacing between objects is too narrow, particularly for objects that are not centrally located.⁵⁶ Wilkinson *et al.* conducted a study to evaluate the impact of visual crowding across four different arrangement conditions (i.e., closed-set grid, widely spaced grid, perimeter, and corners) on latency and fixation to distractors. In each arrangement, symbols were grouped according to grammatical categories, including subjects, actions, objects, and descriptors. The results indicated that participants with Down syndrome were less likely to fixate on irrelevant symbols when the symbols were more widely spaced. However, reducing visual crowding did not lead to an improvement in the latency of symbol searching.⁵⁴

Location of symbols

According to research studies, symbol location is influenced by two key aspects: visual field biases and motor control ability. Visual field biases can impact visual-spatial performance, leading individuals to attend to one-half of the visual field preferentially.^{57,58} For instance, individuals with left-hemisphere dominance often focus more on the right visual field.⁵⁹ Moreover, research indicates that symbols with abstract forms are best positioned on the right side of the display,⁶⁰ whereas symbols depicting emotional facial expressions and geometric configurations are more effectively placed on the left side.^{61,62}

Furthermore, an individual's motor control ability must be assessed to position symbols optimally, ensuring easier access. Beukelman and Light provided an example where frequently used symbols are placed on the side of the display that corresponds to the hand with better motor control.²

Conclusion

The effectiveness of communication for AAC users is significantly influenced by the latency and accuracy of symbol searching. This review article has summarized vital factors that contribute to these aspects, focusing on the design of grid displays that enhance symbol searching efficiency. The primary areas of interest include the organization of symbols, the use of color, visual crowding, and the location of symbols on the grid. By understanding and applying these factors, speech-language pathologists can create more effective AAC systems that improve user communication outcomes. The research highlights the importance of strategic symbol arrangement, appropriate color cues, managing visual crowding, and considering individual visual and motor control abilities in designing grid displays. These insights provide a valuable guideline for optimizing AAC tools to better support users with complex communication needs.

References

- [1] Association AS-L-H. Augmentative and alternative communication (AAC) [cited 2024 July 20]. Available from: <https://www.asha.org/practice-portal/professional-issues/augmentative-and-alternative-communication/>.

- [2] Beukelman D, Light J. Augmentative and alternative communication: Supporting children and adults with complex communication needs. 5th Ed. Pennsylvania: Paul H. Brookes Publishing; 2020.
- [3] Desch LW, Gaebler-Spira D, Council on children with disabilities. Prescribing assistive-technology systems: Focus on children with impaired communication. *Pediatrics*. 2008; 121(6): 1271-80. doi:10.1542/peds.2008-0695.
- [4] Blackstone S, Light J, Beukelman D, Shane H. Visual scene displays. *Augment Comm News*. 2004; 16(2): 1-6.
- [5] Wilkinson KM, Light J. Preliminary investigation of visual attention to human figures in photographs: Potential considerations for the design of aided AAC visual scene displays. *J Speech Lang Hear Res*. 2011; 54(6): 1644-57. doi:10.1044/1092-4388(2011/10-0098).
- [6] Dietz A, McKelvey M, Beukelman DR. Visual scene displays (VSD): New AAC interfaces for persons with aphasia. *Perspect Augment Altern Commun*. 2006; 15(1): 13-7. doi: 10.1044/aac15.1.13.
- [7] Drager KD, Light JC, Speltz JC, Fallon KA, Jeffries LZ. The performance of typically developing 2½-year-olds on dynamic display AAC technologies with different system layouts and language organizations. *J Speech Lang Hear Res*. 2003; 46(2): 298-312. doi: 10.1044/1092-4388(2003/024).
- [8] Drager KD, Light JC, Carlson R, D'Silva K, Larsson B, Pitkin L, Stopper G. Learning of dynamic display AAC technologies by typically developing 3-year-olds. *J Speech Lang Hear Res*. 2004; 47(5): 1133-48. doi: 10.1044/1092-4388(2004/084).
- [9] Drager KD, Light J, Currall J, Muttiah N, Smith V, Kreis D, Nilam-Hall A, Parratt D, Schuessler K, Shermetta K, Wiscount J. AAC technologies with visual scene displays and "just in time" programming and symbolic communication turns expressed by students with severe disability. *J Intellect Dev Disabil*. 2019; 44(3): 321-36. doi: 10.3109/13668250.2017.1326585.
- [10] Holyfield C, Caron JG, Drager K, Light J. Effect of mobile technology featuring visual scene displays and just-in-time programming on communication turns by preadolescent and adolescent beginning communicators. *Int J Speech Lang Pathol*. 2019; 21(2): 201-11. doi: 10.1080/17549507.2018.1441440.
- [11] Higginbotham DJ, Shane H, Russell S, Caves K. Access to AAC: Present, past, and future. *Augment Altern Commun*. 2007; 23(3): 243-57. doi: 10.1080/07434610701571058.
- [12] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Positioning students with cerebral palsy to use augmentative and alternative communication. *Lang Speech Hear Serv Sch*. 1990; 21(1): 15-21. doi: 10.1044/0161-1461.2101.15.
- [13] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Hierarchy of conversational rule violations involving utterance-based augmentative and alternative communication systems. *Augment Altern Commun*. 2008; 24(2): 149-61. doi: 10.1080/07434610802038288
- [14] McCoy KF, Bedrosian JL, Hoag LA, Johnson DE. Brevity and speed of message delivery trade-offs in augmentative and alternative communication. *Augment Altern Commun*. 2007; 23(1): 76-88. doi: 10.1080/07434610600924515.
- [15] Todman J. Rate and quality of conversations using a text-storage AAC system: Single-case training study. *Augment Altern Commun*. 2000; 16(3): 164-79. doi: 10.1080/07434610012331279024.
- [16] Blackstone S. Designing displays: Hints and examples. *Augment Comm News*. 1993; 6(1): 1-6.
- [17] Light J, Lindsay P. Cognitive science and augmentative and alternative communication. *Augment Altern Commun*. 1991; 7(3): 186-203. doi: 10.1080/07434619112331275893.
- [18] Johnson JM, Inglebret E, Jones C, Ray J. Perspectives of speech language pathologists regarding success versus abandonment of AAC. *Augment Altern Commun*. 2006; 22(2): 85-99. doi: 10.1080/07434610500483588.
- [19] Light J, Wilkinson KM, Thiessen A, Beukelman DR, Fager SK. Designing effective AAC displays for individuals with developmental or acquired disabilities: State of the science and future research directions. *Augment Altern Commun*. 2019; 35(1): 42-55. doi: 10.1080/07434618.2018.1558283
- [20] Burke R, Beukelman DR, Hux K. Accuracy, efficiency and preferences of survivors of traumatic brain injury when using three organization strategies to retrieve words. *Brain Inj*. 2004; 18(5): 497-507. doi: 10.1080/02699050310001645784.
- [21] Fitzgerald E, editor. Straight language for the deaf. In: *Proceedings of the Twenty-Eighth Meeting of the Convention of American Instructors of the Deaf*; 1933; West Trenton, New Jersey.
- [22] Dada S, Huguet A, Bornman J. The iconicity of picture communication symbols for children with English additional language and mild intellectual disability. *Augment Altern Commun*. 2013; 29(4): 360-73. doi: 10.3109/07434618.2013.849753.
- [23] Reichle J, York J, Sigafoos J. Implementing augmentative and alternative communication: Strategies for learners with severe disabilities. Pennsylvania: Paul H. Brookes Publishing; 1991.
- [24] Fallon K, Light J, Achenbach A. The semantic organization patterns of young children: Implications for augmentative and alternative communication. *Augment Altern Commun*. 2003; 19(2): 74-85. doi: 10.1080/0743461031000112061.
- [25] Porter G. Pragmatic Organization Dynamic Display Communication Books Direct Access Templates. Cerebral Palsy Education Centre. 2008.
- [26] Dodd JL. Augmentative and alternative communication intervention: an intensive, immersive, socially based service delivery model. California: Plural Publishing; 2017.
- [27] Wilkinson KM, Jagaroo V. Contributions of principles of visual cognitive science to AAC system display design. *Augment Altern Commun*. 2004; 20(3): 123-36. doi: 10.1080/07434610410001699717.

- [28] Wolfe JM. Guided Search 2.0: A revised model of visual search. *Psychon Bull Rev.* 1994; 1: 202-38. doi: 10.3758/BF03200774.
- [29] Wolfe, J., Horowitz, T. What attributes guide the deployment of visual attention and how do they do it?. *Nat Rev Neurosci.* 2004; 5, 495-501. doi: 10.1038/nrn1411.
- [30] Munir F, Cornish KM, Wilding J. A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia.* 2000; 38(9): 1261-70. doi: 10.1016/S0028-3932(00)00036-1.
- [31] Lanfranchi S, Carretti B, Spanò G, Cornoldi C. A specific deficit in visuospatial simultaneous working memory in Down syndrome. *J Intellect Disabil Res.* 2009; 53(5): 474-83. doi: 10.1111/j.1365-2788.2009.01165.x.
- [32] Oi Y, Okuzumi H, Kokubun M. Visuospatial working memory in individuals with intellectual disabilities under simultaneous and sequential presentation. *J Spec Educ Res.* 2018; 7(1): 1-8. doi: 10.6033/spededucation.7.1.
- [33] Bailey BR, Downing J. Using visual accents to enhance attending to communication symbols for students with severe multiple disabilities. *Review.* 1994; 26: 101-19.
- [34] Davidoff J. *Cognition through color.* Massachusetts: The MIT Press; 1991.
- [35] Davidoff J. The neuropsychology of color. In: Hardin CL, Maffi L. *Color categories in thought and language.* New York: Cambridge University Press; 1997.
- [36] Hanna A, Remington R. The representation of color and form in long-term memory. *Memory & Cognition.* 1996; 24(3): 322-30. doi: 10.3758/BF03213296.
- [37] Sperling G, Reeves A, Blaser E, Lu ZL, Weichselgartner E. Two computational models of attention. In: Braun J, Koch C, Davis J, editors. *Visual attention and cortical circuits.* Massachusetts: MIT Press; 2001; 177-214.
- [38] Gegenfurtner KR, Rieger J. Sensory and cognitive contributions of color to the recognition of natural scenes. *Curr Biol.* 2000; 10(13): 805-8.
- [39] Párraga CA, Troscianko T, Tolhurst D. Spatiochromatic properties of natural images and human vision. *Curr Biol.* 2002; 12(6): 483-7.
- [40] Wurm LH, Legge GE, Isenberg LM, Luebker A. Color improves object recognition in normal and low vision. *J Exp Psychol Hum Percept Perform.* 1993; 19(4): 899. doi: 10.1037/0096-1523.19.4.899.
- [41] Schulz MF, Sanocki T. Time course of perceptual grouping by color. *Psychol Sci.* 2003; 14(1): 26-30. doi: 10.1111/1467-9280.0141.
- [42] Wilkinson KM, Carlin M, Jagaroo V. Preschoolers' speed of locating a target symbol under different color conditions. *Augment Altern Commun.* 2006; 22(2): 123-33. doi: 10.1080/07434610500483620.
- [43] Wilkinson K, Carlin M, Thistle J. The role of color cues in facilitating accurate and rapid location of aided symbols by children with and without Down syndrome. *Am J Speech Lang Pathol.* 2008; 17(2): 179-93. doi: 10.1044/1058-0360(2008/018).
- [44] Thistle JJ, Wilkinson K. The effects of color cues on typically developing preschoolers' speed of locating a target line drawing: Implications for augmentative and alternative communication display design. *Am J Speech Lang Pathol.* 2009; 18(3): 231-40. doi: 10.1044/1058-0360(2009/08-0029).
- [45] Wilkinson KM, O'Neill T, McIlvane WJ. Eye-tracking measures reveal how changes in the design of aided AAC displays influence the efficiency of locating symbols by school-age children without disabilities. *J Speech Lang Hear Res.* 2014; 57(2): 455-66. doi: 10.1044/2013_JSLHR-L-12-0159.
- [46] Wilkinson KM, Madel M. Eye tracking measures reveal how changes in the design of displays for augmentative and alternative communication influence visual search in individuals with Down syndrome or autism spectrum disorder. *Am J Speech Lang Pathol.* 2019; 28(4): 1649-58. doi: 10.1044/2019_AJSLP-19-0006.
- [47] Wilkinson KM, McIlvane WJ. Perceptual factors influence visual search for meaningful symbols in individuals with intellectual disabilities and Down syndrome or autism spectrum disorders. *Am J Intellect Dev Disabil.* 2013; 118(5): 353-64. doi: 10.1352/1944-7558-118.5.353.
- [48] Hetzroni O, Ne'eman A. Influence of color on acquisition and generalization of graphic symbols. *J Intellect Disabil Res.* 2013; 57(7): 669-80. doi: 10.1111/j.1365-2788.2012.01584.x.
- [49] Wilkinson KM, Coombs B. Preliminary exploration of the effect of background color on the speed and accuracy of search for an aided symbol target by typically developing preschoolers. *Early Child Serv (San Diego).* 2010; 4(3): 171-83. PMID: 26457074.
- [50] Wilkinson KM, Snell J. Facilitating children's ability to distinguish symbols for emotions: The effects of background color cues and spatial arrangement of symbols on accuracy and speed of search. *Am J Speech Lang Pathol.* 2011; 20(4): 288-301. doi: 10.1044/1058-0360(2011/10-0065).
- [51] Wilkinson K, Weiss A. Background color cues do not facilitate attention to single symbols by individuals with Down syndrome. Poster presentation at: Annual Conference of the American Speech-Language Hearing Association (ASHA); 2017 Nov; Los Angeles, CA.
- [52] Thistle JJ, Wilkinson K. Effects of background color and symbol arrangement cues on construction of multi-symbol messages by young children without disabilities: Implications for aided AAC design. *Augment Altern Commun.* 2017; 33(3): 160-9. doi: 10.1080/07434618.2017.1336571.
- [53] Bialystok E. *Factors in the growth of linguistic awareness. Where Language Meets Thought.* New York. Routledge. 1986; 5-25.
- [54] Wilkinson KM, Gilmore R, Qian Y. Judicious arrangement of symbols on a simulated augmentative and alternative communication display optimizes visual attention by individuals with Down syndrome. *J Speech Lang Hear Res.* 2022; 65(2): 710-26. doi: 10.1044/2021_JSLHR-21-00278.

- [55] Bulakowski PF, Post RB, Whitney D. Reexamining the possible benefits of visual crowding: Dissociating crowding from ensemble percepts. *Atten Percept Psychophys.* 2011; 73(4): 1003-9. doi: 10.3758/s13414-010-0086-2.
- [56] Keshvari S, Rosenholtz R. Pooling of continuous features provides a unifying account of crowding. *J Vis.* 2016; 16(3): 1-15. doi: 10.1167/16.3.39.
- [57] Kinsbourne M. *Neuropsychology of attention.* Neuropsychology. Amsterdam: Elsevier; 1994: 105-23.
- [58] Reuter-Lorenz PA, Kinsbourne M, Moscovitch M. Hemispheric control of spatial attention. *Brain Cogn.* 1990; 12(2): 240-66.
- [59] Mesulam M-M. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci.* 1999; 354(1387): 1325-46. doi: 10.1098/rstb.1999.0482.
- [60] Kosslyn SM. Seeing and imagining in the cerebral hemispheres: A computational approach. In: *Readings in Cognitive Science: A Perspective from Psychology and Artificial Intelligence.* Amsterdam: Elsevier; 2013; 615-42. doi: 10.1016/B978-1-4832-1446-7.50052-2.
- [61] Pizzagalli D, Regard M, Lehmann D. Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport.* 1999; 10(13): 2691-8.
- [62] Sergent J, Signoret J-L. Varieties of functional deficits in prosopagnosia. *Cereb Cortex.* 1992; 2(5): 375-88. doi: 10.1093/cercor/2.5.375.



Review article: Designing grid displays in AAC systems to enhance accuracy and reduce latency in symbol searching

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ABSTRACT

Augmentative and Alternative Communication (AAC) systems support individuals with complex communication needs. This review article examines factors influencing the design of grid displays in AAC systems to enhance symbol searching accuracy and reduce latency. Four key areas are identified: the organization of symbols, color cues, visual crowding, and symbol location. Effective symbol organization, such as semantic-syntactic and schematic displays, can facilitate efficient communication, while color cues may improve visual attention and memory recall. Managing visual crowding and strategically placing symbols based on visual field biases and motor control abilities are also crucial. By optimizing these elements, speech-language pathologists can develop AAC displays that improve user communication outcomes. The findings provide guidelines for designing user-centered AAC systems tailored to individual cognitive, motor, and sensory needs.

Introduction

Augmentative and alternative communication (AAC) is a field of clinical practice that serves the demands of individuals with complex communication needs, which are defined by deficiencies in an expressive mode (e.g., speaking and writing) and/or a receptive mode of communication (e.g., spoken language comprehension). The communication competence of those individuals fails to meet their communication needs in various circumstances (e.g., communicating with unfamiliar communication partners and/or environments, noisy environments, group talking, etc.). The impairments that feasibly result in complex communication needs may include congenital disabilities (e.g., cerebral palsy, developmental apraxia of speech, etc.), acquired disabilities (e.g., amyotrophic lateral sclerosis, stroke, etc.), or neurological differences (e.g., autistic spectrum disorders, down syndrome, etc.).^{1,2}

There are two main types of AAC systems: Unaided and aided. Unaided systems involve AAC modes that do not require an external tool. These systems include gestures, vocalizations, finger spelling, manual signs, facial expressions, etc. Aided systems, on the other hand, require external tools. These systems include writing, photographs, natural objects, communication boards, etc. Aided systems also come in three forms: low-tech (i.e., nonelectronic AAC forms), such as writing, natural objects, and communication boards; mid-tech (i.e., battery-powered electronic AAC forms), such as single-button-communication switches and GoTalk³, and high-tech (i.e., electronic AAC

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forms with more advanced processors) such as Tablet-based speech-output technologies and speech generating devices.^{1,2}

There are two significant types of display layout used in picture-based AAC systems (e.g., communication boards/books, drawings (or line drawings), speech-generating devices, etc.): Visual scene display (VSD) and grid. VSD embedded vocabulary concepts within natural scenes (i.e., typically photographs) according to each AAC user's life. Vocabulary words are represented in pictures, and vocabulary words in each category are grouped in each scene.⁴⁻⁶ For example, in the kitchen scene, vocabulary words such as stove, kettle, fridge, cooking, and hungry are embedded. In contrast, the grid layout presents vocabulary words as graphic symbols arranged in rows and columns in a grid pattern. Each grid contains a single graphic symbol and is isolated in physical space.²

Different display layouts may influence the efficiency of AAC for communication. For instance, it has been reported that VSD is more uncomplicated to learning than grid layout for beginning communicators and young children.⁷⁻¹⁰ The AAC display's design should promote users' ability to communicate. Communication proficiency may include the user's motivation,^{11,12} vocabulary words corresponding to their needs and interests,² communication speed and accuracy,^{2,13-15} and other factors. To design the AAC display to support communication competence, many research studies revealed that the display should be created by the individual's cognitive/linguistic, literacy, motor, sensory, and perceptual abilities.¹⁶⁻¹⁸ Otherwise, an unsuitable AAC display design might impose additional demands on users to create messages, leading to challenges and frustration for the user and communication partners.¹⁹

The latency and accuracy of symbol searching are among the key factors significantly contributing to

AAC users' communication effectiveness. Many studies have explored the elements that impact the latency and accuracy of symbol searching. This review article intends to report and summarize the factors in designing the grid displays that enhance AAC users' latency and accuracy, providing a guideline for speech-language pathologists. According to the review, there are four primary areas of research interest related to symbol searching latency and accuracy when designing grid displays: (a) Strategies for organizing symbols, (b) Color of symbols, (c) Visual crowding, and (d) Location of symbols.

Strategies for organizing symbols

This domain concerns how symbols are arranged on a page to facilitate efficient symbol searches. Currently, there are seven types of symbol organization: (a) Semantic-syntactic, (b) Schematic, (c) Taxonomic, (d) Pragmatically organized displays, (e) Alphabetical, (f) Chronological, and (g) Idiosyncratic. Each type possesses distinct characteristics, necessitating careful decision-making to match the organization to individuals' abilities and preferences. For example, Burke, Beukelman, and Hux reported that participants with traumatic brain injury (TBI) preferred to use schematic grid displays despite showing better communication competency when using alphabetic grid displays.²⁰

A semantic-syntactic grid displays organized symbols according to syntactic functions (i.e., part of speech). Each page contains various types of words. Following Fitzgerald's Key Format, subjects, verbs, adjectives, objects, places, times, and so on are arranged from left to right, respectively.²¹ This organization is designed to promote language learning in individuals with complex communication needs.² The depiction of semantic-syntactic grid displays is shown in Figure 1.



Figure 1. Semantic-syntactic grid displays.

The symbols were sourced from ARASAAC and designed by Sergio Palao.

Schematic grid displays, also called activity grid displays, organize symbols based on activity themes such as routines, zoo visits, birthday parties, gardening, and other activities. Each page includes nouns (e.g., people, places, animals, plants), verbs, and prepositions related to the theme. An example of a schematic grid display is shown in Figure 2. Research studies suggest that schematic grid displays facilitate AAC symbol learning.^{22,23} However, there are two main disadvantages to this type of display. First, the exact vocabulary words may

repeatedly appear on different pages, leading to increased memory load in high-tech devices (e.g., smartphones and tablets) and added weight in low-tech AAC forms (e.g., communication boards). Second, this arrangement reduces the automaticity of learning using the AAC system, as users must individually learn the different locations of the target word (i.e., symbol) on each schematic page. It is recommended that schematic pages be combined with semantic-syntactic grid displays.²

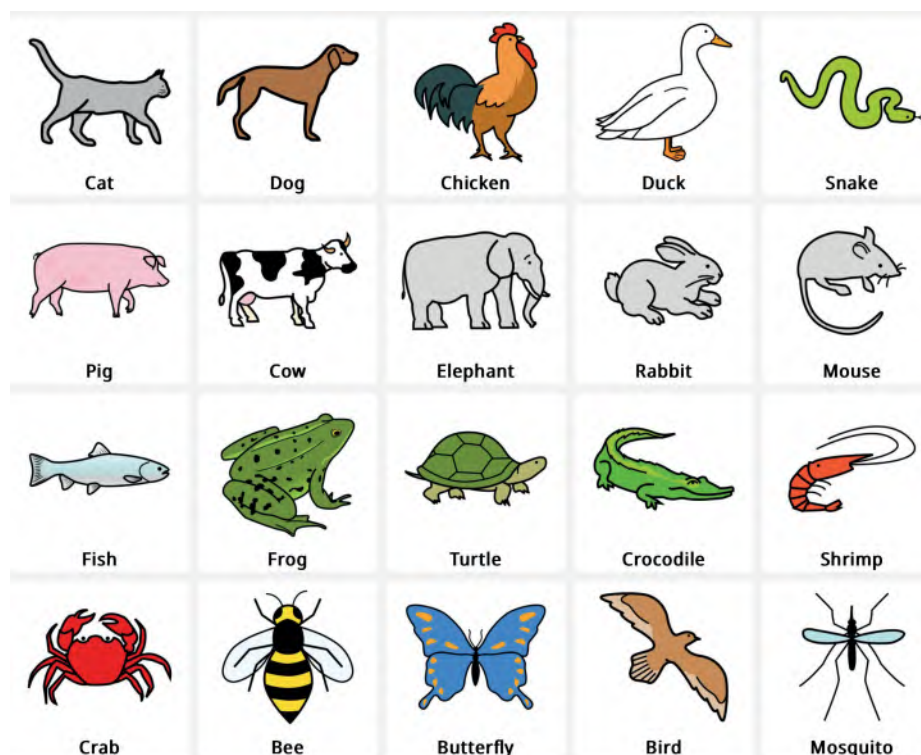


Figure 2. The schematic grid displays the animal theme.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The taxonomic grid displays symbols in categories such as fruits, animals, family members, places, clothes, action words, and so on. This type of display requires users to comprehend the concept of categorization, making it unsuitable for individuals younger than six or seven years old.²⁴ Furthermore, taxonomic grid displays have a significant drawback, as they necessitate extensive navigation between pages to find target words. Consequently, this display format may be appropriate for individuals with complex communication needs who use AAC to supplement their speech to clarify specific words rather than relying on AAC as their primary means of communication.²

Pragmatically organized displays incorporate multiple types of display organization to mitigate the limitations of each type, such as the time-consuming

nature of searching for target symbols. By integrating semantic-syntactic, taxonomic, and schematic grid displays, the time spent searching for symbols within specific conversational contexts—such as discussing a visit to the zoo—can be reduced. Examples of systems using this type of organization include Pragmatic Organization Dynamic Displays (PODD), Voco Chat, and Snap Core First, each offering unique features. For instance, PODD is the inclusion of a navigation page, which directs users to the target symbols through page tabs such as the main page (i.e., semantic-syntactic), food category (i.e., taxonomic), ordering food (i.e., schematic), conversational repair (i.e., taxonomic), and so on.²⁵ An example of PODD is illustrated in Figure 3. The primary disadvantage of this type of display is the potential for the exact words or symbols to appear repeatedly across multiple pages.²



Figure 3. Starter page of Pragmatic Organization Dynamic Displays (PODD).
The symbols were sourced from ARASAAC and designed by Sergio Palao.

An alphabetic grid displays organized symbols in alphabetical order. For instance, the first page contains words starting with “A,” and the second page includes words beginning with “B,” and so forth. This organization may be appropriate for literate individuals. Moreover, this display format might be ideal for individuals with complex communication needs who use AAC to enhance their speech by clarifying specific words rather than using AAC as their primary mode of communication.²

Chronological grid displays, also known as visual schedules or calendar systems, organize activities in sequential order, either in rows or columns. This arrangement helps individuals follow a structured sequence of tasks, reducing challenging behaviors that may arise during activity transitions.^{2,26} An example of a chronological grid display is Figure 4.

Idiosyncratic grid displays are personalized arrangements of symbols tailored to an individual’s unique preferences, needs, or interests that fit their cognitive organization or abilities, such as organizing by favorite movies, personal pets, etc. These displays are customized to align with the user’s communication style and requirements.²



Figure 4. Chronological grid displays related to the morning routine.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

Color of the symbols

Many cognitive factors affect how successfully AAC users employ grid display, but visual cognition is the factor that contributes most in terms of grid display.²⁷⁻²⁹ Visuospatial processing is considered the primary skill needed to use visually-based aided AAC systems.²⁷ Visuospatial processing is integral visual skills, including symbol perception (i.e., the ability to notice the presence of a symbol on a display), symbol discrimination (i.e., the ability to distinguish between two symbols on a display), identification (i.e., the ability to recognize what a symbol represents), and recall (i.e., ability to remember where the symbol is located on display).^{27,28} Individuals with developmental and intellectual disabilities frequently experience difficulty inhibiting their attention to distracting stimuli.^{30,31} This challenge may be related to issues about visuospatial processing, especially visuospatial working memory.^{31,32} To reduce this issue, researchers examine the effects of color cues on symbol learning in children with and without disabilities.

Research has shown that the use of color can have a positive impact on processing and aiding the learning of symbol meaning for children with multiple disabilities.^{27,33-35} These findings were supported by evidence that color facilitates image retrieval.^{27,36,37} Visual short-term memory may be improved when distinct colors represent different features of an object.³⁸ Long-term visual memory is strengthened when specific colors and forms are associated with memory representation.³⁶ In addition, Párraga *et al.* indicated that color can influence attention and enhance perception speed.³⁹ Therefore, numerous studies have investigated the impact of color on attention and the speed of target symbol searching, focusing on two primary aspects: the internal symbol color and the symbol

background color.

Internal symbol color attracts attention, differentiates between similar objects, and facilitates object recognition.⁴⁰ Moreover, surface color can aid in the grouping of objects.⁴¹ According to these findings, many researchers intended to investigate whether the internal symbol color could increase the speed and accuracy of locating the symbol in grid displays when the like-colored symbols were grouped. Most research outcomes showed that grouping symbols with similar colors improves the efficiency of finding the symbol in the array.⁴²⁻⁴⁶ This might be because clustering like-colored symbols decreases cognitive load and enhances visual attention.^{42,43,45,47}

For example, Wilkinson and Madel measured the gaze pattern of six children with Down syndrome and six children with autism by using eye-tracking technology. The results demonstrated that participants significantly focused on target symbols while fixating less on distractors when the like-colored symbols were clustered together. An example of internal color cues with a clustering arrangement is illustrated in Figure 5. Nevertheless, Hetzroni and Ne'eman's research findings indicated that all four preschoolers with autism showed no differences in success in learning recognition of the new vocabulary, regardless of the level of color (i.e., grey-scale symbols versus color symbols) included in the symbols.⁴⁸ Although clustering symbols on the array that shared internal color could improve symbol searching accuracy and reduce latency, there was a notable limitation. The number of symbols that do not share the same internal color makes it impossible to arrange them by clustering based on internal color. Consequently, some researchers explored the effects of background color cues on the accuracy and latency of the symbol-searching process.

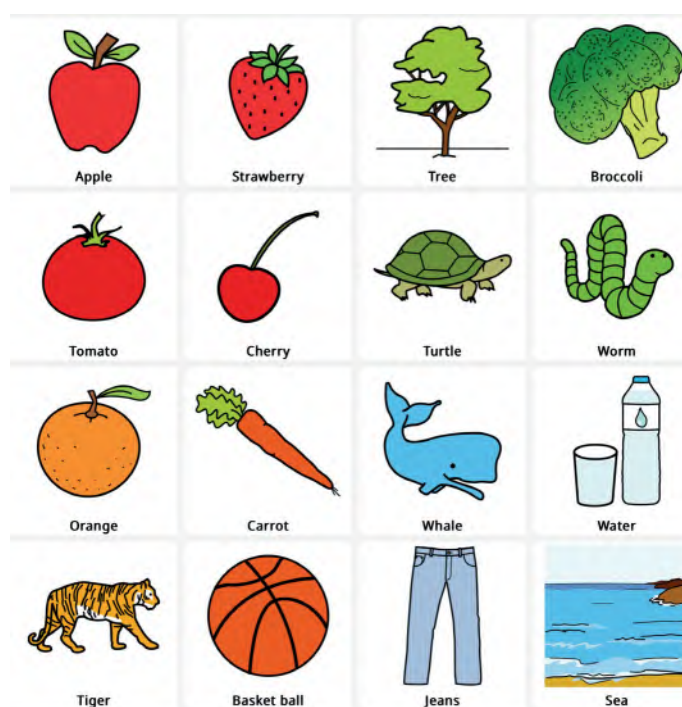


Figure 5. Internal color cues with a clustering arrangement.
The symbols were sourced from ARASAAC and designed by Sergio Palao.

The influence of symbol background color was examined concerning two primary effects: (a) the speed of identifying individual symbols functioning as a semantic cue, and (b) the speed of identifying a sequence of symbols (i.e., for constructing multi-symbol messages) functioning as a syntactic cue. Most research studies have shown that background color cues do not improve the speed or accuracy of single symbol searching in children with typical development^{44,49,50} or Down syndrome.⁵¹ For example, Wilkinson and Snell investigated whether background color cueing helps children with typical development identify emotion symbols grouped by valence. The results indicated that background color did not enhance the children's ability to identify symbols more quickly.⁵⁰ These studies reported that background color cues related to semantics neither provided any advantage in searching nor slowed down the process of locating a single symbol due to the distracting effect. However, One study demonstrated that symbol background color increased the speed of single symbol searching in adults without disabilities and recommended using background color cues with communication partners to assist individuals who rely on AAC in locating target symbols on a grid display.⁵²

Likewise, in terms of using background colors as a syntactic cue (e.g., word-class categories such as red background for pronouns, blue background for action verbs, yellow background for adverbs, etc.), studies reported that background color cues did not aid multi-symbol message construction in young children. This might be because background color cueing as a syntactic cue might be linked to metalinguistic skills, typically emerging between 5 and 7 years of age.⁵³ Therefore, employing background color cueing to enhance sentence construction may only benefit older individuals with intact metalinguistic awareness.⁵² However, Wilkinson *et al.* reported that background color cueing reduced the latency in locating the target symbol. This may be attributed to the fact that the participants in the study were adults with Down syndrome, whose average receptive vocabulary age was approximately 7 years and 0 months.⁵⁴ The illustration of using background-color cueing as a syntactic cue is shown in Figure 1.

The impact of background color cues remains a subject of ongoing research. The researchers suggest that the lack of benefit from background color cues in young children may be due to the increased cognitive load imposed by the need to interpret the color cues, a skill that young children may not yet possess.⁵⁰ This aligns with Wilkinson and Jagaroo's assertion that the effectiveness of color cues depends on the user's cognitive abilities and the complexity of the visual display.²⁷

Visual crowding

Visual crowding or clutter refers to a phenomenon where symbols become indistinguishable due to proximity. In a standard grid display, multiple rows and columns of symbols are arranged adjacently, without intervening space, and with uniform dimensions. This configuration leads to difficulties in distinguishing individual elements, limits eye and hand movement, and impedes visual

search efficiency.^{19,55} The recognition of an object is hindered when the spacing between objects is too narrow, particularly for objects that are not centrally located.⁵⁶ Wilkinson *et al.* conducted a study to evaluate the impact of visual crowding across four different arrangement conditions (i.e., closed-set grid, widely spaced grid, perimeter, and corners) on latency and fixation to distractors. In each arrangement, symbols were grouped according to grammatical categories, including subjects, actions, objects, and descriptors. The results indicated that participants with Down syndrome were less likely to fixate on irrelevant symbols when the symbols were more widely spaced. However, reducing visual crowding did not lead to an improvement in the latency of symbol searching.⁵⁴

Location of symbols

According to research studies, symbol location is influenced by two key aspects: visual field biases and motor control ability. Visual field biases can impact visual-spatial performance, leading individuals to attend to one-half of the visual field preferentially.^{57,58} For instance, individuals with left-hemisphere dominance often focus more on the right visual field.⁵⁹ Moreover, research indicates that symbols with abstract forms are best positioned on the right side of the display,⁶⁰ whereas symbols depicting emotional facial expressions and geometric configurations are more effectively placed on the left side.^{61,62}

Furthermore, an individual's motor control ability must be assessed to position symbols optimally, ensuring easier access. Beukelman and Light provided an example where frequently used symbols are placed on the side of the display that corresponds to the hand with better motor control.²

Conclusion

The effectiveness of communication for AAC users is significantly influenced by the latency and accuracy of symbol searching. This review article has summarized vital factors that contribute to these aspects, focusing on the design of grid displays that enhance symbol searching efficiency. The primary areas of interest include the organization of symbols, the use of color, visual crowding, and the location of symbols on the grid. By understanding and applying these factors, speech-language pathologists can create more effective AAC systems that improve user communication outcomes. The research highlights the importance of strategic symbol arrangement, appropriate color cues, managing visual crowding, and considering individual visual and motor control abilities in designing grid displays. These insights provide a valuable guideline for optimizing AAC tools to better support users with complex communication needs.

References

- [1] Association AS-L-H. Augmentative and alternative communication (AAC) [cited 2024 July 20]. Available from: <https://www.asha.org/practice-portal/professional-issues/augmentative-and-alternative-communication/>.

- [2] Beukelman D, Light J. Augmentative and alternative communication: Supporting children and adults with complex communication needs. 5th Ed. Pennsylvania: Paul H. Brookes Publishing; 2020.
- [3] Desch LW, Gaebler-Spira D, Council on children with disabilities. Prescribing assistive-technology systems: Focus on children with impaired communication. *Pediatrics*. 2008; 121(6): 1271-80. doi:10.1542/peds.2008-0695.
- [4] Blackstone S, Light J, Beukelman D, Shane H. Visual scene displays. *Augment Comm News*. 2004; 16(2): 1-6.
- [5] Wilkinson KM, Light J. Preliminary investigation of visual attention to human figures in photographs: Potential considerations for the design of aided AAC visual scene displays. *J Speech Lang Hear Res*. 2011; 54(6): 1644-57. doi:10.1044/1092-4388(2011/10-0098).
- [6] Dietz A, McKelvey M, Beukelman DR. Visual scene displays (VSD): New AAC interfaces for persons with aphasia. *Perspect Augment Altern Commun*. 2006; 15(1): 13-7. doi: 10.1044/aac15.1.13.
- [7] Drager KD, Light JC, Speltz JC, Fallon KA, Jeffries LZ. The performance of typically developing 2½-year-olds on dynamic display AAC technologies with different system layouts and language organizations. *J Speech Lang Hear Res*. 2003; 46(2): 298-312. doi: 10.1044/1092-4388(2003/024).
- [8] Drager KD, Light JC, Carlson R, D'Silva K, Larsson B, Pitkin L, Stopper G. Learning of dynamic display AAC technologies by typically developing 3-year-olds. *J Speech Lang Hear Res*. 2004; 47(5): 1133-48. doi: 10.1044/1092-4388(2004/084).
- [9] Drager KD, Light J, Currall J, Muttiah N, Smith V, Kreis D, Nilam-Hall A, Parratt D, Schuessler K, Shermetta K, Wiscount J. AAC technologies with visual scene displays and "just in time" programming and symbolic communication turns expressed by students with severe disability. *J Intellect Dev Disabil*. 2019; 44(3): 321-36. doi: 10.3109/13668250.2017.1326585.
- [10] Holyfield C, Caron JG, Drager K, Light J. Effect of mobile technology featuring visual scene displays and just-in-time programming on communication turns by preadolescent and adolescent beginning communicators. *Int J Speech Lang Pathol*. 2019; 21(2): 201-11. doi: 10.1080/17549507.2018.1441440.
- [11] Higginbotham DJ, Shane H, Russell S, Caves K. Access to AAC: Present, past, and future. *Augment Altern Commun*. 2007; 23(3): 243-57. doi: 10.1080/07434610701571058.
- [12] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Positioning students with cerebral palsy to use augmentative and alternative communication. *Lang Speech Hear Serv Sch*. 1990; 21(1): 15-21. doi: 10.1044/0161-1461.2101.15.
- [13] Hoag LA, Bedrosian JL, McCoy KF, Johnson DE. Hierarchy of conversational rule violations involving utterance-based augmentative and alternative communication systems. *Augment Altern Commun*. 2008; 24(2): 149-61. doi: 10.1080/07434610802038288
- [14] McCoy KF, Bedrosian JL, Hoag LA, Johnson DE. Brevity and speed of message delivery trade-offs in augmentative and alternative communication. *Augment Altern Commun*. 2007; 23(1): 76-88. doi: 10.1080/07434610600924515.
- [15] Todman J. Rate and quality of conversations using a text-storage AAC system: Single-case training study. *Augment Altern Commun*. 2000; 16(3): 164-79. doi: 10.1080/07434610012331279024.
- [16] Blackstone S. Designing displays: Hints and examples. *Augment Comm News*. 1993; 6(1): 1-6.
- [17] Light J, Lindsay P. Cognitive science and augmentative and alternative communication. *Augment Altern Commun*. 1991; 7(3): 186-203. doi: 10.1080/07434619112331275893.
- [18] Johnson JM, Inglebret E, Jones C, Ray J. Perspectives of speech language pathologists regarding success versus abandonment of AAC. *Augment Altern Commun*. 2006; 22(2): 85-99. doi: 10.1080/07434610500483588.
- [19] Light J, Wilkinson KM, Thiessen A, Beukelman DR, Fager SK. Designing effective AAC displays for individuals with developmental or acquired disabilities: State of the science and future research directions. *Augment Altern Commun*. 2019; 35(1): 42-55. doi: 10.1080/07434618.2018.1558283
- [20] Burke R, Beukelman DR, Hux K. Accuracy, efficiency and preferences of survivors of traumatic brain injury when using three organization strategies to retrieve words. *Brain Inj*. 2004; 18(5): 497-507. doi: 10.1080/02699050310001645784.
- [21] Fitzgerald E, editor. Straight language for the deaf. In: *Proceedings of the Twenty-Eighth Meeting of the Convention of American Instructors of the Deaf*; 1933; West Trenton, New Jersey.
- [22] Dada S, Huguet A, Bornman J. The iconicity of picture communication symbols for children with English additional language and mild intellectual disability. *Augment Altern Commun*. 2013; 29(4): 360-73. doi: 10.3109/07434618.2013.849753.
- [23] Reichle J, York J, Sigafoos J. Implementing augmentative and alternative communication: Strategies for learners with severe disabilities. Pennsylvania: Paul H. Brookes Publishing; 1991.
- [24] Fallon K, Light J, Achenbach A. The semantic organization patterns of young children: Implications for augmentative and alternative communication. *Augment Altern Commun*. 2003; 19(2): 74-85. doi: 10.1080/0743461031000112061.
- [25] Porter G. Pragmatic Organization Dynamic Display Communication Books Direct Access Templates. Cerebral Palsy Education Centre. 2008.
- [26] Dodd JL. Augmentative and alternative communication intervention: an intensive, immersive, socially based service delivery model. California: Plural Publishing; 2017.
- [27] Wilkinson KM, Jagaroo V. Contributions of principles of visual cognitive science to AAC system display design. *Augment Altern Commun*. 2004; 20(3): 123-36. doi: 10.1080/07434610410001699717.

- [28] Wolfe JM. Guided Search 2.0: A revised model of visual search. *Psychon Bull Rev.* 1994; 1: 202-38. doi: 10.3758/BF03200774.
- [29] Wolfe, J., Horowitz, T. What attributes guide the deployment of visual attention and how do they do it?. *Nat Rev Neurosci.* 2004; 5, 495-501. doi: 10.1038/nrn1411.
- [30] Munir F, Cornish KM, Wilding J. A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia.* 2000; 38(9): 1261-70. doi: 10.1016/S0028-3932(00)00036-1.
- [31] Lanfranchi S, Carretti B, Spanò G, Cornoldi C. A specific deficit in visuospatial simultaneous working memory in Down syndrome. *J Intellect Disabil Res.* 2009; 53(5): 474-83. doi: 10.1111/j.1365-2788.2009.01165.x.
- [32] Oi Y, Okuzumi H, Kokubun M. Visuospatial working memory in individuals with intellectual disabilities under simultaneous and sequential presentation. *J Spec Educ Res.* 2018; 7(1): 1-8. doi: 10.6033/specialeducation.7.1.
- [33] Bailey BR, Downing J. Using visual accents to enhance attending to communication symbols for students with severe multiple disabilities. *Review.* 1994; 26: 101-19.
- [34] Davidoff J. Cognition through color. Massachusetts: The MIT Press; 1991.
- [35] Davidoff J. The neuropsychology of color. In: Hardin CL, Maffi L. Color categories in thought and language. New York: Cambridge University Press; 1997.
- [36] Hanna A, Remington R. The representation of color and form in long-term memory. *Memory & Cognition.* 1996; 24(3): 322-30. doi: 10.3758/BF03213296.
- [37] Sperling G, Reeves A, Blaser E, Lu ZL, Weichselgartner E. Two computational models of attention. In: Braun J, Koch C, Davis J, editors. Visual attention and cortical circuits. Massachusetts: MIT Press; 2001; 177-214.
- [38] Gegenfurtner KR, Rieger J. Sensory and cognitive contributions of color to the recognition of natural scenes. *Curr Biol.* 2000; 10(13): 805-8.
- [39] Párraga CA, Troscianko T, Tolhurst D. Spatiochromatic properties of natural images and human vision. *Curr Biol.* 2002; 12(6): 483-7.
- [40] Wurm LH, Legge GE, Isenberg LM, Luebker A. Color improves object recognition in normal and low vision. *J Exp Psychol Hum Percept Perform.* 1993; 19(4): 899. doi: 10.1037/0096-1523.19.4.899.
- [41] Schulz MF, Sanocki T. Time course of perceptual grouping by color. *Psychol Sci.* 2003; 14(1): 26-30. doi: 10.1111/1467-9280.0141.
- [42] Wilkinson KM, Carlin M, Jagaroo V. Preschoolers' speed of locating a target symbol under different color conditions. *Augment Altern Commun.* 2006; 22(2): 123-33. doi: 10.1080/07434610500483620.
- [43] Wilkinson K, Carlin M, Thistle J. The role of color cues in facilitating accurate and rapid location of aided symbols by children with and without Down syndrome. *Am J Speech Lang Pathol.* 2008; 17(2): 179-93. doi: 10.1044/1058-0360(2008/018).
- [44] Thistle JJ, Wilkinson K. The effects of color cues on typically developing preschoolers' speed of locating a target line drawing: Implications for augmentative and alternative communication display design. *Am J Speech Lang Pathol.* 2009; 18(3): 231-40. doi: 10.1044/1058-0360(2009/08-0029).
- [45] Wilkinson KM, O'Neill T, McIlvane WJ. Eye-tracking measures reveal how changes in the design of aided AAC displays influence the efficiency of locating symbols by school-age children without disabilities. *J Speech Lang Hear Res.* 2014; 57(2): 455-66. doi: 10.1044/2013_JSLHR-L-12-0159.
- [46] Wilkinson KM, Madel M. Eye tracking measures reveal how changes in the design of displays for augmentative and alternative communication influence visual search in individuals with Down syndrome or autism spectrum disorder. *Am J Speech Lang Pathol.* 2019; 28(4): 1649-58. doi: 10.1044/2019_AJSLP-19-0006.
- [47] Wilkinson KM, McIlvane WJ. Perceptual factors influence visual search for meaningful symbols in individuals with intellectual disabilities and Down syndrome or autism spectrum disorders. *Am J Intellect Dev Disabil.* 2013; 118(5): 353-64. doi: 10.1352/1944-7558-118.5.353.
- [48] Hetzroni O, Ne'eman A. Influence of color on acquisition and generalization of graphic symbols. *J Intellect Disabil Res.* 2013; 57(7): 669-80. doi: 10.1111/j.1365-2788.2012.01584.x.
- [49] Wilkinson KM, Coombs B. Preliminary exploration of the effect of background color on the speed and accuracy of search for an aided symbol target by typically developing preschoolers. *Early Child Serv (San Diego).* 2010; 4(3): 171-83. PMID: 26457074.
- [50] Wilkinson KM, Snell J. Facilitating children's ability to distinguish symbols for emotions: The effects of background color cues and spatial arrangement of symbols on accuracy and speed of search. *Am J Speech Lang Pathol.* 2011; 20(4): 288-301. doi: 10.1044/1058-0360(2011/10-0065).
- [51] Wilkinson K, Weiss A. Background color cues do not facilitate attention to single symbols by individuals with Down syndrome. Poster presentation at: Annual Conference of the American Speech-Language Hearing Association (ASHA); 2017 Nov; Los Angeles, CA.
- [52] Thistle JJ, Wilkinson K. Effects of background color and symbol arrangement cues on construction of multi-symbol messages by young children without disabilities: Implications for aided AAC design. *Augment Altern Commun.* 2017; 33(3): 160-9. doi: 10.1080/07434618.2017.1336571.
- [53] Bialystok E. Factors in the growth of linguistic awareness. *Where Language Meets Thought.* New York. Routledge. 1986; 5-25.
- [54] Wilkinson KM, Gilmore R, Qian Y. Judicious arrangement of symbols on a simulated augmentative and alternative communication display optimizes visual attention by individuals with Down syndrome. *J Speech Lang Hear Res.* 2022; 65(2): 710-26. doi: 10.1044/2021_JSLHR-21-00278.

- [55] Bulakowski PF, Post RB, Whitney D. Reexamining the possible benefits of visual crowding: Dissociating crowding from ensemble percepts. *Atten Percept Psychophys.* 2011; 73(4): 1003-9. doi: 10.3758/s13414-010-0086-2.
- [56] Keshvari S, Rosenholtz R. Pooling of continuous features provides a unifying account of crowding. *J Vis.* 2016; 16(3): 1-15. doi: 10.1167/16.3.39.
- [57] Kinsbourne M. *Neuropsychology of attention.* Neuropsychology. Amsterdam: Elsevier; 1994: 105-23.
- [58] Reuter-Lorenz PA, Kinsbourne M, Moscovitch M. Hemispheric control of spatial attention. *Brain Cogn.* 1990; 12(2): 240-66.
- [59] Mesulam M-M. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci.* 1999; 354(1387): 1325-46. doi: 10.1098/rstb.1999.0482.
- [60] Kosslyn SM. Seeing and imagining in the cerebral hemispheres: A computational approach. In: *Readings in Cognitive Science: A Perspective from Psychology and Artificial Intelligence.* Amsterdam: Elsevier; 2013; 615-42. doi: 10.1016/B978-1-4832-1446-7.50052-2.
- [61] Pizzagalli D, Regard M, Lehmann D. Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport.* 1999; 10(13): 2691-8.
- [62] Sergent J, Signoret J-L. Varieties of functional deficits in prosopagnosia. *Cereb Cortex.* 1992; 2(5): 375-88. doi: 10.1093/cercor/2.5.375.

Application for acoustic assessment: A pilot study in Parkinson's patients

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ABSTRACT

Background: Patients with Parkinson's disease (PD) often experience speech impairment that impacts their daily lives. The evaluation of abnormal voice qualities involves the use of both objective and subjective assessments. Subjective assessments encompass auditory-perceptual assessment and self-reports provided by the patient. On the other hand, objective evaluations include endoscopic images, aerodynamic assessments, and acoustic analyses. In speech therapy for PD patients, acoustic assessment provides accurate information to evaluate acoustic characteristics and support rehabilitation programs. However, access to acoustic assessment instruments is limited in Thailand due to their high price and lack of portability.

Objective: This study aimed to develop an Application for Acoustic Assessment (AAA) and to conduct a pilot study of the application among healthy aging (HA) and aging PD subjects.

Materials and methods: This study was a developmental research design comprising three phases. Phase one focused on the development of the AAA and the evaluation of the accuracy and precision of the application. A comparative analysis was conducted between AAA and Praat, a speech analysis software package, in phase two, among twenty HA. Five acoustic parameters, loudness, jitter, shimmer, high frequency (Hf_o), and low frequency (Lf_o), were used to determine concurrent validity. Phase three compared AAA and Praat with twenty aging PD subjects, examining the concurrent validity and test-retest reliability and comparing the acoustic parameters of HA users with those of the aging PD cohort.

Results: In phase one, the AAA shows vital accuracy ranging from 96.86% to 99.59% and high precision, with a Coefficient of Variation (%CV) of 1.65%-3.78%. In phase two, the concurrent validity of AAA compared with Praat in HA exhibited significant and very strong correlations ($r_s \geq 0.90$, $p < 0.001$) in all acoustic parameters, except for shimmer, which showed substantial and robust correlations ($r_s = 0.73$, $p < 0.001$). In phase three, the concurrent validity of AAA compared with Praat in aging PD subjects exhibited significant and very strong correlations ($r_s \geq 0.90$, $p < 0.001$) in loudness, Hf_o , and Lf_o , whereas substantial and robust correlations were shown in jitter ($r_s = 0.85$, $p < 0.001$) and shimmer ($r_s = 0.82$, $p < 0.001$). The Intraclass Correlation Coefficient (ICC) exhibited excellent reliability in all acoustic parameters ($r > 0.90$). When comparing the HA and aging PD subjects using AAA, significant differences ($p < 0.05$) were observed in all acoustic parameters, except for Lf_o ($p = 0.55$).

Conclusion: The AAA demonstrates high concurrent validity and reliability. It can effectively be utilized for PD group testing as an alternative tool for evaluating acoustic characteristics and aiding in treatment planning.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, following Alzheimer's disease (AD) in prevalence, that is predominant among the group of neurodegenerative movement disorders.¹ It is found in approximately 1% of individuals aged over 60 years.² In Thailand, the prevalence of PD was 706 per 100,000 people aged over 50 years.³ Additionally, hypokinetic dysarthria, which is a motor speech disorder, is found in approximately 89% of PD patients.^{4,5} This symptom causes phonation, articulation, and prosody abnormalities, leading to hypophonia, monotone speech, reduced speech intelligibility, and imprecise articulation.⁵⁻⁷ In a study by Rusz *et al.*, it was demonstrated that 78% of untreated PD patients show abnormalities in phonation, articulation, and prosody.⁸ Additionally, in acoustic parameter tests, a study by Fox and Ramig showed that the PD group exhibited decreased loudness compared to the healthy group.⁹ Meanwhile, Suphinnapong *et al.* found that jitter and shimmer were higher in the PD group than in the healthy group.¹⁰ These speech abnormalities lead to difficulties in social interaction and daily activities and a diminished quality of life. Additionally, these communication challenges often lead to a loss of confidence, prompting behaviors that avoid social interaction.⁷

Evaluation of abnormal voice qualities can be divided into subjective and objective evaluation. The subjective evaluation uses auditory-perceptual assessment, where listeners rate voice quality using scales such as GRBAS or CAPE-V, and self-evaluation of voice quality by the patient such as Voice Handicap Index (VHI).^{11,12} In contrast, objective evaluation uses instruments to assess voice abnormalities, including endoscopic imaging, aerodynamic assessment, and acoustic assessment.¹³ In acoustic assessment, characteristics such as loudness, jitter, shimmer, maximum vocal frequency, and minimum vocal frequency are typically evaluated.^{11,13}

One commonly used tool for acoustic assessment is the Computerized Speech Lab (CSL™), which can evaluate various acoustic characteristics. However, its high price and lack of portability remain limiting factors in Thailand.¹⁴ In contrast, the Dr. Speech tool offers a more affordable alternative to CSL™ and can assess acoustic characteristics. However, it, too, remains relatively costly in Thailand. Alternatively, Praat, an open-source software package, is commonly used for acoustic analysis in research and clinical settings. It has the advantage of being free of charge, offering many features for acoustic analysis, and allowing customization through scripts. However, it requires regular updates to ensure uninterrupted functionality, cannot display results in real-time, and has a complex graphical user interface.¹⁵

Therefore, this study aims to develop an Application for Acoustic Assessment (AAA), a non-profit tool for evaluating voice abnormalities in Parkinson's patients. This application will assess acoustic parameters such as loudness, voice quality (jitter and shimmer), and pitch [high frequency (Hf_0) and low frequency (Lf_0)]. It is designed to be compatible with multiple operating systems, portable on Android smartphones or tablets, user-friendly, and cost-effective for a pilot study group.

Materials and methods

Study design

This research was developmental, aiming to develop AAA. The purpose of AAA is to evaluate acoustic characteristics, including loudness, jitter, shimmer, Hf_0 , and Lf_0 , in healthy aging (HA) and aging PD subjects.

This study was divided into three phases: 1) developing the AAA and assessing its accuracy and precision in a laboratory setting, 2) evaluating the concurrent validity of the AAA in HA subjects, and 3) investigating the concurrent validity and reliability of the AAA in aging PD subjects. The acoustic parameters between AAA and Praat were also compared between the HA and PD groups. The testing protocol was conducted following the standards set by the American Speech-Language-Hearing Association (ASHA).¹³ All data collection occurred in a soundproof room using an ATR-2500X-USB microphone positioned 8 cm from the mouth. The AAA acoustic data were collected via a tablet (Teclast M40Pro, Android 11), while the Praat data were collected using a laptop computer (Praat version 6.1.51).

Phase 1: Development of AAA

The researchers designed the layout of the AAA by studying the operational principles of currently employed tools for acoustic assessment and conducting a literature review. Then, the ideas were discussed with the advisor, and the selected ideas were used to develop the AAA together with a co-advisor at the Biomedical Engineering Institute (BMEI), Chiang Mai University. The AAA was designed to evaluate loudness, jitter, shimmer, Hf_0 , and Lf_0 using an Android tablet. The researchers utilized the openSMILE 3.0 program,¹⁶ software designed for extracting sound features from audio and music signals.

The researchers studied the accuracy and precision tests of the AAA at the BMEI Lab, Chiang Mai University, by performing vocal tasks. These tasks involved sustained phonation of /ah/ in a comfortable voice, at maximum loudness, average speech volume, high pitch, and low pitch, with each phonation lasting at least 3 to 5 seconds (Table 1). A comparison was conducted between AAA and Praat to assess accuracy. Each vocal task was repeated 10 times with a 1-minute rest during the precision test before moving on to the next test.

Table 1. List of the vocal tasks.

Task code	Speech data
[TASK 1]	Sustained phonation of /ah/ as loud as possible in a comfortable voice as constant and long as possible, at least 3-5 sec. This task was performed in one breath.
[TASK 2]	Sustained phonation of /ah/ at a normal speech volume in a comfortable pitch with loudness as constant and long as possible, at least 3-5 sec. This task was performed in one breath.
[TASK 3]	Sustained phonation of /ah/ at the highest pitch in a comfortable voice as constant and long as possible, at least 3-5 sec. This task was performed in one breath.
[TASK 4]	Sustained phonation of /ah/ at the lowest pitch in a comfortable voice as constant and long as possible, at least 3-5 sec. This task was performed in one breath.

Phase 2: Test of concurrent validity in HA

In this phase, concurrent validity testing was conducted among HA within the Faculty of Associated Medical Sciences, Chiang Mai University. Twenty HA were purposively selected based on the following inclusion criteria: 1) aged between 50 to 75 years; 2) understanding and use of Thai as their primary language for speaking, reading, and writing; 3) no neurological diseases, cognitive impairment, hearing loss, vision problems, or abnormal speech according to medical records; and 4) able to independently provide consent to participate in the research. Each of the acoustic parameters was evaluated with the same vocal tasks as those in phase one, first with AAA, then followed by Praat. Tests were conducted in the soundproof room at the Speech Clinic, Department of Occupational Therapy, Faculty of Associated Medical Sciences, Chiang Mai University. Each test was performed three times, and the best results were selected for analysis. The microphone was positioned 8 cm from the mouth. There was a 1-minute rest period between each task and a 5-minute rest before proceeding to the next test. Participants were excluded if they were unable to complete the testing process.

Phase 3: Test of concurrent validity and reliability in PD subjects

In this phase, concurrent validity and reliability testing were conducted by purposively selecting twenty PD subjects from the Parkinson's Clinic at the Northern Neuroscience Center, Faculty of Medicine, Chiang Mai University, and the Neurology Clinic, Department of Medicine, Mukdahan Hospital. The inclusion criteria were as follows:

- 1) Aged between 50 and 75 years.
- 2) Diagnosis as PD by a neurologist.
- 3) Using Thai as the primary language for speaking, reading, and writing.
- 4) No symptoms of Parkinsonism were observed that could be attributed to diseases other than Parkinson's disease.
- 5) No history of hearing loss or, if applicable, usage of a hearing aid meeting the standards recommended by an audiologist.
- 6) There is no history of vision problems, or if vision problems are present, the use of eyeglasses to aid vision is permitted.

- 7) No depression based on obtaining a score of <7 from 9 questions on the depression screening assessment (9Q) with either no symptoms of depression or very few symptoms (total score <7).¹⁷
- 8) No cognitive impairment was determined by using the Mental State Examination T10 (MSET10);¹⁸ without meeting the criteria for suspected cognitive impairment, inclusion is based on the cutoff point criteria for scores as follows: for aging adults not attending school, a score of ≤ 14 ; for aging adults attending primary school, a score of ≤ 17 ; for aging adults attending education beyond primary school, a score of ≤ 22 .
- 9) Must be capable of independently providing consent to participate in the research.

Subsequently, the test proceeded as in phase two. There were two additional rounds of testing to determine the test-retest reliability in the AAA section. In this phase, we compared the acoustic parameters of HA subjects from phase two with those obtained from the PD subjects in phase three. Participants were excluded if they were unable to complete the testing process

Statistical analysis

All data underwent statistical analysis using SPSS (IBM Corp. Released 2022. IBM SPSS Statistics for Mac, Version 29.0. Armonk, NY: IBM Corp).¹⁹ In phase one, we utilized accuracy and precision to examine the AAA. In phases two and three, concurrent validity between AAA and Praat was analyzed using Spearman's correlation. In phase three, the test-retest reliability of AAA was assessed using the Intraclass Correlation Coefficient (ICC) with a two-way mixed effects model for multiple raters/measurements. The Wilcoxon signed-rank test was used to compare acoustic parameters between the HA and PD subjects.

Results**Phase 1: Development of the AAA**

The AAA is divided into two main parts: the processing part and the display and recording part. The processing part was developed using openSMILE version 3.0.¹⁶ The variables selected for evaluation included loudness, jitter, shimmer, Hf_0 , and Lf_0 . The audio data was imported using a condenser microphone (ATR-2500X-USB) (Figure 1).



Figure 1. Condenser microphone (ATR-2500-USB). a: AAA icon, b: participant data recording part.

In the display and recording part, the display section is shown as a graph and can record audio for replay. Evaluation is conducted based on the processing

part (Figure 2). Data is stored under user accounts in the recording section, and evaluation results are recorded for each assessment. The data are stored on the tablet's internal storage. In this study, the Teclast M40Pro running

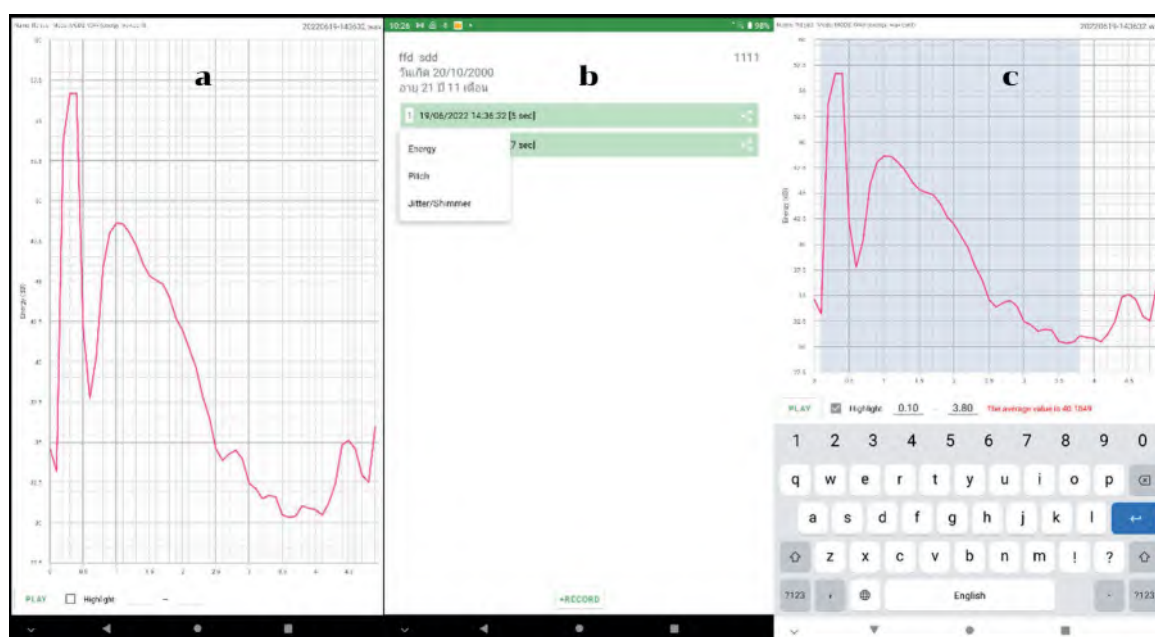


Figure 2. An example of an AAA in the display section. a: test results graph, b: display of acoustic parameters for analysis, c: selection of the times period for analysis.

Android 11 was utilized.

Assessing the accuracy of AAA involves calculating the percentage of accuracy compared to Praat.²⁰ The results show that the AAA achieved a percent accuracy ranging from 96.86 to 99.59, indicating that AAA has a similar value to Praat, which also exceeds 95% accuracy. In the precision test, we calculated the Coefficient of Variation (%CV) to assess the precision of the AAA.²⁰ The results show that the %CV for the AAA ranges from 1.65 to 3.78, within the acceptable limit of 5%, indicating that it can be used in clinical assessment.

Phase 2: Test concurrent validity in HA

Spearman's correlations were conducted between AAA and Praat to assess the concurrent validity of the acoustic parameters in HA group aged 50-70 years (9 males, 11 females) (Table 2).²¹ The results demonstrated significant and strong correlations, mainly observed in loudness ($r_s=0.94$, $p<0.001$), jitter ($r_s=0.94$, $p<0.001$), Hf_0 ($r_s=0.98$, $p<0.001$), and Lf_0 ($r_s=0.98$, $p<0.001$). Additionally, a significant and strong correlation was demonstrated in shimmer ($r_s=0.73$, $p<0.001$) (Table 3).

Table 2. Demographic data of participants.

	HA (N=20)		PD (N=20)	
Number (N)	M	F	M	F
	9	11	15	5
Age (year)	61 (5.49)		64 (5.54)	
Age min-max (year)	50-70		54-74	

Note: age is expressed by mean (SD), M: male, F: female

Table 3. Concurrent validity in the HA and PD groups.

	HA (N=20)				PD (N=20)					
	Median (min, max)		Median difference	r_s	p value	Median (min, max)		Median difference	r_s	p value
	AAA	Praat				AAA	Praat			
Loudness (dB)	68.75 (61.34, 75.53)	68.52 (62.01, 77.66)	0.23	0.94	<0.001**	65.56 (54.63, 72.16)	64.61 (54.67, 71.74)	1.05	0.95	<0.001**
Jitter (%)	0.49 (0.30, 0.68)	0.46 (0.30, 0.64)	0.03	0.94	<0.001**	0.53 (0.18, 1.52)	0.48 (0.18, 1.47)	0.05	0.85	<0.001**
Shimmer (%)	4.93 (2.73, 7.28)	5.40 (3.22, 7.65)	-0.47	0.73	<0.001**	6.21 (3.26, 13.19)	6.59 (2.06, 13.14)	-0.38	0.82	<0.001**
Hf ₀ (Hz)	254.89 (167.67, 440.45)	241.79 (163.74, 445.93)	13.10	0.98	<0.001**	214.18 (152.50, 307.21)	159.09 (153.03, 315.77)	55.09	0.94	<0.001**
Lf ₀ (Hz)	179.65 (95.61, 227.07)	179.40 (81.45, 229.56)	0.25	0.98	<0.001**	162.11 (115.88, 217.09)	138.15 (120.60, 218.60)	23.96	0.98	<0.001**

Note : * $p < 0.05$, ** $p < 0.001$

Phase 3: Test of concurrent validity and reliability in PD subjects

In the PD group aged 54-74 years (15 males, 5 females) (Table 2), significant and very strong correlations between AAA and Praat using Spearman's correlation were mainly observed in loudness ($r_s = 0.95$, $p < 0.001$), Hf₀ ($r_s = 0.94$,

$p < 0.001$), and Lf₀ ($r_s = 0.98$, $p < 0.001$). Additionally, significant and robust correlations were demonstrated in jitter ($r_s = 0.85$, $p < 0.001$) and shimmer ($r_s = 0.82$, $p < 0.001$) (Table 3). ICC²² was used to assess the test-retest reliability of AAA in the PD group. Significant and excellent ICC were demonstrated in all acoustic parameters (Table 4).

Table 4. Test-retest reliability of the acoustic parameters in PD using AAA.

Test-retest reliability (%)	Intraclass correlation ^b	95% CI		F Test with true value 0			
		Lower	Upper	Value	df1	df2	sig
Loudness (dB)	0.98 ^c	0.95	0.99	49.04	19	38	0.00*
jitter (%)	0.95 ^c	0.90	0.98	22.69	19	38	0.00*
shimmer (%)	0.95 ^c	0.91	0.98	23.85	19	38	0.00*
Hf ₀ (Hz)	0.99 ^c	0.97	0.99	95.30	19	38	0.00*
Lf ₀ (Hz)	0.98 ^c	0.97	0.99	76.58	19	38	0.00*

Note: Two-way mixed effects model where people effects are random, and measures effects are fixed, b: type C intraclass correlation coefficients using a consistency definition, The between-measure variance is excluded from the denominator variance, c: this estimate is computed assuming the interaction effect is absent because it is not estimable otherwise.

Comparisons of the acoustic parameters between HA and aging PD subjects using the Wilcoxon signed rank test revealed significant differences in all acoustic parameters except for Lf₀ (179.65 Hz vs. 162.11 Hz, $p = 0.55$), whereas Loudness (68.75 dB vs. 65.56 dB,

$p < 0.001$), and Hf₀ (254.89 Hz vs. 214.18 Hz, $p < 0.001$) were higher in HA than in the aging PD subjects. Additionally, jitter (0.49% vs. 0.53%, $p = 0.04$) and shimmer (4.93% vs. 6.21%, $p = 0.03$) were lower in HA than in the aging PD subjects (Table 5).

Table 5. Acoustic analysis for HA and PD using AAA.

	HA (N=20)	PD (N=20)	Median difference	95% confident interval		p value
	Median (min, max)	Median (min, max)		Lower	Upper	
Loudness (dB)	68.75 (61.35, 75.54)	65.56 (54.63, 72.16)	3.19	-7.61	-1.85	<0.001**
Jitter (%)	0.49 (0.30, 0.68)	0.53 (0.18, 1.52)	-0.04	0.00	0.20	0.04*
Shimmer (%)	4.93 (2.73, 7.28)	6.21 (3.26, 13.19)	-1.28	0.14	2.91	0.03*
Hf ₀ (Hz)	254.89 (167.67, 440.45)	214.18 (152.50, 307.21)	40.71	-74.80	-16.36	<0.001**
Lf ₀ (Hz)	179.65 (95.61, 227.07)	162.11 (115.88, 217.09)	17.54	-31.93	15.36	0.55

Note: * $p < 0.05$, ** $p < 0.001$

Discussion

In this study, we developed and designed an AAA for instrumental assessment of voice by ASHA.¹⁵ In laboratory testing, the AAA has high accuracy and precision higher than 95% or 0.95, which is widely accepted in medical research.²³

The concurrent validity of the acoustic characteristics in AAA compared with Praat in both the HA and PD groups demonstrated significant and very strong correlations, except for shimmer in the HA group and jitter and shimmer in the PD group, which showed substantial and robust correlations (Table 3). In the test-retest reliability analysis, the AAA also demonstrated significant and excellent ICC in all acoustic parameters of the PD group (Table 4). In the test results, it was found that the results obtained from AAA were almost all higher than those from Praat, as per the study by Maryn *et al.*, which demonstrated that, in a comparison between Praat and the Multi-Dimensional Voice Program (MDVP), the results obtained from Praat were lower than those from MDVP.²⁴ As observed in the study by Vaz-Freitas *et al.* Praat, MDVP, VoiceStudio, and Dr. Speech were tested, and the results obtained from Praat were consistently lower.²⁵ Previous studies suggest that Praat generally yields lower measurements than other programs, except for jitter and shimmer, for which Praat has higher measurements than Dr. Speech. These findings are consistent with the results of this current research. This demonstrates that AAA can be used for acoustic assessment on par with other instruments. Additionally, the researcher plans to collaborate with BMEI to develop AAA to enhance tools such as tremor voice analysis. This collaboration seeks to achieve more comprehensive results by including data collection on subjects with other types of voice disorders, such as hoarseness, amyotrophic lateral sclerosis, and presbyphonia, in future studies.

The main abnormalities in the PD group include the following: 1) a decrease in loudness, which is attributed to incomplete closure of the vocal cords, creating space between the vocal folds; 2) tremor, breathiness, and hoarseness of voice, as it was also found that higher jitter

and shimmer were present due to decreased flexibility and reduced coordination of vocal cord movement; and 3) speaking in a monotone with no pitch and having lower frequencies than usual, which is a condition caused by a decreased ability to control the air pressure under the larynx, which affects pitch control.^{8-9,26} In this study, when comparing the results obtained from the AAA between the HA and PD groups, voice abnormalities in PD with significant differences in all acoustic parameters except for Lf₀ were demonstrated (Table 5). In a study by Fox and Ramig, it was shown that there was a decrease in loudness in the PD group compared to the HA group.²⁶ Furthermore, in the study by Suphinnapong *et al.*, the PD group exhibited significantly higher levels of jitter and shimmer compared to the healthy group,¹⁰ whereas the decrease in Hf₀ and Lf₀ can be attributed to the limited pitch control of PD.²⁶

Limitations

The present study did not investigate the duration or severity of Parkinson's disease, including other symptoms in patients. Additionally, this study only collected data from the PD group and did not include different groups of patients with voice disorders.

Conclusion

This research aimed to develop and test an AAA that evaluates acoustic characteristics, including loudness, jitter, shimmer, Hf₀, and Lf₀, by sustaining the vowel / ah/. The test results indicate that the AAA can effectively assess voice abnormalities associated with aging PD subjects in this pilot study. In this regard, the AAA is convenient for mobility as it is utilized via a tablet, which is a portable device. The program incurs no cost as it was developed using open-source technology and yields accurate evaluation results. The researchers anticipate this AAA will be an alternative tool for evaluating acoustic characteristics. Finally, researchers should focus on gathering data from other voice disorder groups in future work.

Ethical approval

This study was approved by the Research Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University (Approval ID: AMSEC-65EX-027), the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (Study code: None-2565-0004 Research ID:0004), and the Ethics Committee for Human Research of Mukdahan Hospital (Approval ID: MEC 25/66). All participants received the complete necessary information related to the research, and informed written consent was obtained before their enrollment into the study.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

- [1] Olanow CW, Stocchi F, Lang AE. The dopaminergic and non-dopaminergic features of Parkinson's disease. In: Olanow CW, Stocchi F, Lang AE, editors. *Parkinson's disease*. Chichester: Wiley-Blackwell; 2011. p. 1-6.
- [2] Rego AC, Cardoso SM, Oliveira CR. Molecular pathways of mitochondrial dysfunction in neurodegeneration: the paradigms of parkinson's and huntington's diseases. In: Malva JO, Rego AC, Cunha RA, Oliveira CR, editors. *Interaction between neurons and glia in aging and disease*. Boston: Springer; 2007. p. 193-219.
- [3] Muangpaisan W, Siritipakorn P, Assantachai P. Development of a Thai parkinson's disease screening tool and the prevalence of parkinsonism and parkinson's disease, based on a community survey in Bangkok. *Neuroepidemiology*. 2017; 49: 74-81. doi:10.1159/000480510.
- [4] Muñoz-Vigueras N, Prados-Román E, Valenza MC, Granados-Santiago M, Cabrera-Martos I, Rodríguez-Torres J, et al. Speech and language therapy treatment on hypokinetic dysarthria in parkinson disease: systematic review and meta-analysis. *Clin Rehabil*. 2020; 35: 639-55. doi:10.1177/0269215520976267.
- [5] Galáž Z, Mekyska J, Zvoncak V, Mucha J, Kiska T, Smekal Z, et al. Changes in phonation and their relations with progress of Parkinson's disease. *Appl Sci*. 2018; 8: 2339. doi:10.3390/app8122339.
- [6] Duffy JR. Hypokinetic Dysarthria. In Duffy JR, editor. *Motor speech disorders: substrates, differential diagnosis, and management*. 3rd Ed. St. Louis: Elsevier /Mosby; 2013: p. 165-89.
- [7] Pinto S, Ozsancak C, Tripoliti E, Thobois S, Limousin-Dowsey P, Auzou P. Treatments for dysarthria in parkinson's disease. *Lancet Neurol*. 2004; 3: 547-56. doi:10.1016/S1474-4422(04)00854-3.
- [8] Fox CM, Ramig LO. Vocal sound pressure level and self-perception of speech and voice in men and women with idiopathic parkinson disease. *Am J Speech Lang Pathol*. 1997; 6: 85-94. doi:10.1044/1058-0360.0602.85.
- [9] Ruz J, Cmejla R, Ruzickova H, Ruzicka E. Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated parkinson's disease. *J Acoust Soc Am*. 2011; 129: 350-67. doi:10.1121/1.3514381.
- [10] Suphinnapong P, Phokaewvarangkul O, Thubthong N, Teeramongkonrasmee A, Mahattanasakul P, Lorwattanapongsa P, et al. Objective vowel sound characteristics and their relationship with motor dysfunction in Asian parkinson's disease patients. *J Neurol Sci*. 2021; 426: 117487. doi:10.1016/j.jns.2021.117487.
- [11] Dejonckere PH, Bradley P, Clemente P, Cornut G, Crevier-Buchman L, Friedrich G, et al. A basic protocol for functional assessment of voice pathology, especially for investigating the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the committee on phoniatrics of the European Laryngological Society (ELS). *Eur Arch Otorhinolaryngol*. 2001; 258: 77-82. doi: 10.1007/s004050000299.
- [12] Mehta DD, Hillman RE. Voice assessment: updates on perceptual, acoustic, aerodynamic, and endoscopic imaging methods. *Curr Opin Otolaryngol Head Neck Surg*. 2008; 16: 211-5. doi:10.1097/MOO.0b013e-3282fe96ce.
- [13] Patel RR, Awan SN, Barkmeier-Kraemer J, Courey M, Deliyski D, Eadie T, et al. Recommended protocols for instrumental assessment of voice: American speech-language-hearing association expert panel to develop a protocol for instrumental assessment of vocal function. *Am J Speech Lang Pathol*. 2018; 27: 887-905. doi:10.1044/2018_AJSLP-17-0009.
- [14] Chiamonte R, Bonfiglio M. Acoustic analysis of voice in parkinson's disease: a systematic review of voice disability and meta-analysis of studies. *Rev Neurol*. 2020; 70: 393-405. doi:10.33588/rn.7011.2019414.
- [15] Maryn Y. Practical acoustics in clinical voice assessment: a Praat primer. *Perspect ASHA Spec Interest Groups*. 2017; 2: 14-32. doi:10.1044/persp2.SIG3.14.
- [16] Eyben F, Weninger F, Gross F, Schuller B. Recent developments in openSMILE, the munich open-source multimedia feature extractor. In: Jaimes A, Sebe N, Boujemaa N, editors. *Proceedings of the 21st ACM international conference on multimedia*; 2013 Oct 21-25. Barcelona, Spain. New York: Association for Computing Machinery; 2013. p. 835-53.
- [17] Department of Mental Health. Guidebook of depressive disorders surveillance and care: provincial level. 3rd Ed, Rev. Ubon Ratchathani: Department of Mental Health; 2014. (in Thai)
- [18] Prasert Boongird. Interesting story about dementia [internet]. 2018 [cited 2024 May 14]. Available from: https://w1.med.cmu.ac.th/anes/wp-content/uploads/2020/10/Newsletter_MSET10-2.pdf. (in Thai)
- [19] IBM. How to cite IBM SPSS Statistics or earlier versions of SPSS 2014 [internet]. 2014 [cited 2024 May 24]. Available from: <https://www.ibm.com/support/pages/how-citeibm-spss-statistics-or-earlier-versions-spss>.

- [20] Navaphattra Nunak, Taweepol Suesut. Measurement and instrumentation: application in the food industry. Bangkok: KMITL School of Engineering; 2012. (in Thai)
- [21] Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences 3rd Ed. Boston, MA: Houghton Mifflin; 1994
- [22] Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016; 15: 155-63. doi:10.1016/j.jcm.2016.02.012.
- [23] Hazra A. Using the confidence interval confidently. J Thorac Dis. 2017; 9: 4124-9. doi:10.21037/jtd.2017.09.14.
- [24] Maryn Y, Roy N, De Bodt M, Van Cauwenberge P, Corthals P. Acoustic measurement of overall voice quality: a meta-analysis. J Acoust Soc Am. 2009; 126: 2619-34. doi:10.1121/1.3224706.
- [25] Vaz-Freitas S, Pestana PM, Almeida V, Ferreira A. Acoustic analysis of voice signal: comparison of four applications software. Biomed Signal Process Control. 2018; 40: 318-23. doi:10.1016/j.bspc.2017.09.031.
- [26] Trail M, Fox C, Ramig LO, Sapir S, Howard J, Lai EC. Speech treatment for parkinson's disease. Neuro Rehabilitation. 2005; 20: 205-21. doi:10.3233/NRE-2005-20307.

Sensory processing and social participation in children with autism spectrum disorder: A systematic review

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ABSTRACT

Background: Children with autism spectrum disorder experience various challenges, in which difficulties in social participation represent a significant area of concern. Research studies indicate that autistic children who experience more challenges in sensory processing tend to demonstrate lower social competence. Therefore, a comprehensive synthesis of the evidence exploring the link between sensory processing and social participation is needed to develop targeted interventions and support strategies to enhance social functioning in children with autism spectrum disorder.

Objective: This systematic review aimed to investigate the impact of sensory processing on social participation in children with ASD aged 3-18 years.

Materials and methods: The review involved a comprehensive search across electronic databases such as Scopus, PubMed, and OTseeker. The McMaster Critical Review Form for Quantitative Studies was used to evaluate the methodological quality of the included articles.

Results: A total of 4,158 records were identified through database searches and manual searches. Following the title and abstract review, 10 studies were selected for the full-text review, which led to the inclusion of 8 studies in the systematic review that met the predefined criteria. Among the 8 studies, 7 studies reported a significant correlation between sensory processing and social participation in children with ASD. Specifically, sensory over-responsivity, under-responsivity, and seeking behaviors were found to influence the child's ability to comprehend, interpret, and respond to social cues effectively, thereby increasing the social challenges commonly associated with ASD.

Conclusion: This systematic review underscores the evident impact of sensory processing difficulties on social participation among children with ASD. It highlights the critical role of sensory processing in facilitating successful social functioning across diverse contexts and emphasizes its importance in enhancing overall social well-being in children with ASD.

Introduction

Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental condition that significantly impacts an individual's ability to participate in social activities across various contexts.¹ Children with ASD often face a combination of social communication difficulties, behavioral challenges, and sensory processing (SP) differences that can affect their ability to engage meaningfully in everyday activities.¹ Among the numerous challenges experienced by autistic children, difficulties in social participation represent a significant area of concern. Research studies have found that communication deficits

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and behavioral problems can interfere significantly with social participation in children with ASD.^{2,4} Difficulties in verbal and non-verbal communication, such as limited expressive and receptive language skills and problems in understanding social cues, impact the child's ability to engage in social interactions.^{2,3} Moreover, behavioral challenges such as repetitive behaviors, restricted interests, and difficulties regulating emotions can further limit a child's participation in various social contexts, including school and community activities.⁴ The presence of co-occurring conditions, such as anxiety and depression, can also impact social engagement in children with ASD.⁵ While social communication and behavioral challenges are hallmark features of ASD, recent research has increasingly highlighted the importance of sensory processing in shaping the experiences and social participation of children with ASD.^{6,7}

Sensory processing refers to the brain's ability to receive, interpret, and respond to sensory information from the environment, facilitating adaptive responses.⁸ SP difficulties are highly prevalent in children with ASD, with studies indicating that up to 95% of children diagnosed with ASD experience challenges in this area.⁹ SP difficulties can manifest as sensory over-responsivity (SOR), sensory under-responsivity (SUR), and sensory seeking (SS).¹⁰ Children with SOR may exhibit increased responses to sensory inputs, such as sound or touch, while those with SUR may show limited or no response to stimuli that would typically elicit a reaction. On the other hand, children with SS may actively seek out sensory experiences, often in unusual ways.¹⁰ These sensory processing differences can profoundly impact how individuals with ASD engage with their environment, potentially influencing various aspects of their daily functioning.^{7,11}

Effective social participation—the ability to engage in social activities and interactions within various environments such as home, school, and community—is crucial for children's emotional, cognitive, and adaptive development. It also plays a vital role in forming meaningful relationships, learning, and overall well-being.^{1,12,13} Children with ASD often experience difficulties in navigating social interactions, understanding social cues, and establishing and maintaining relationships.¹⁴ Effective social participation requires individuals to interpret social cues, engage in reciprocal communication, and regulate emotions, which can be challenging when SP challenges are present.⁸ For instance, a child hypersensitive to noise may avoid social settings like classrooms or playgrounds. In contrast, another who craves sensory input might engage in behaviors that others find disruptive or inappropriate, further hindering social interaction. Moreover, children with sensory processing differences are linked to challenges in social play and interactions across different developmental stages. In early childhood, sensory processing differences, such as difficulties in processing visual, tactile, proprioceptive, and vestibular information, are associated with challenges in social play activities, including sharing and playing cooperatively.¹⁵ As children progress to middle childhood, those with SI differences

are likelier to engage in solitary play and may not shift to organized games with rules as their typically developing peers do.¹⁶ Additionally, children with SI difficulties tend to have more limited social networks and spend less time with friends compared to peers without these difficulties.¹⁷

Research suggests that children with ASD who experience more significant sensory processing difficulties often demonstrate lower social competence and face more significant barriers to social engagement.^{18,19} Therefore, a comprehensive review of the available evidence on how SP influences social participation in individuals with autism is needed. This review will enhance the understanding of the complex relationship between SP and social participation in children with ASD, which helps in developing tailored interventions and support strategies that effectively address the unique needs of individuals with ASD. The aim of this review is to investigate the impact of SP on social participation in children with ASD aged 3-18 years. The age range of 3 to 18 years was selected for this study to include the critical developmental stages where sensory processing and social participation are most relevant and observable. The starting age of 3 was chosen because it is typically when a diagnosis of ASD is first made, allowing for early identification and intervention, which is crucial for improving developmental outcomes. At this age, children also begin engaging in structured social environments, such as preschools, where social participation can be effectively observed. Including children up to age 18 enables a comprehensive analysis of how sensory processing challenges affect social participation across early childhood to adolescence, supporting the development of targeted interventions.

Materials and methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. This systematic review was prospectively registered with PROSPERO under the identification number CRD42023457686. A comprehensive search for relevant studies was conducted across databases, including Scopus, PubMed, and OTseeker. A manual search of printed journals such as the American Journal of Occupational Therapy, the British Journal of Occupational Therapy, the Canadian Journal of Occupational Therapy, and the Australian Journal of Occupational Therapy was undertaken to ensure comprehensive inclusion of the literature.

Search strategy

The following keywords were used during the database searches:

- **Population-Related Terms:** “autism spectrum disorder”, “autism”, “Asperger syndrome”, “pervasive developmental disorder”.
- **Social-Related Terms:** “social”, “community”, “social skills”, “social participation”, “community participation”, “social engagement”, “social functioning”, “social experience”, “social behavior”.
- **Sensory processing-Related Terms:** “sensory

processing", "sensory integration", "sensory processing disorder", "sensory integration disorder", "sensory reactivity", "sensory over-responsivity", "sensory under-responsivity", "sensory seeking", "sensory avoiding", "sensory sensitivity", "low registration".

Inclusion and exclusion criteria

The studies included in this review were required to meet specific inclusion criteria: (1) the studies must involve children aged 3 to 18 years diagnosed with Autism Spectrum Disorder (ASD) as the primary population, (2) the studies focused on the relationship between sensory processing/integration and social participation, (3) studies that were published between January 2013 and July 2023, (4) peer-reviewed studies, (5) the full text of the studies had to be available, and (6) studies published in English. Studies were excluded if they presented level 4 evidence (case reports and case series) or level 5 evidence (expert opinions).

Quality assessment

The methodological quality of the included studies was assessed using the McMaster Critical Review Form for Quantitative Studies.²⁰ This form comprises 16 items that evaluate various aspects of the study's methodology, including its objective, literature review, methodology, results, and conclusion. Each item is assigned a score of "one" if it meets specific criteria and "zero" if it does not. The total score, ranging from 0 to 16, determines the methodological quality classification of the study. Scores between 0-8 are considered poor, 9-10 are deemed fair, 11-12 are considered good, 13-14 are considered very good, and 15-16 are considered excellent.²¹ This critical appraisal tool demonstrates good inter-rater reliability, ensuring consistent and reliable assessments.²¹

Data extraction

Eight studies matched the inclusion criteria and were included in the systematic review. Information regarding the author(s), publication year, aims and objectives, study design, sample characteristics, assessments utilized to measure sensory processing and social participation, and findings was extracted from each of the included studies and organized into a tabulated format.

Study selection process

The study selection process was designed to be thorough and minimize bias. First, two authors

independently reviewed the titles and abstracts of the studies to determine if they met the inclusion criteria. Studies that appeared eligible were then subjected to a full-text review. At this stage, studies were excluded if they did not focus on the target population, did not address the relationship between sensory processing and social participation, or did not meet other inclusion criteria. If there were disagreements about whether to include or exclude a study, independent reviewers re-evaluated the study to ensure an accurate decision. Following the full-text review, the risk of bias in each included study was assessed using the McMaster Critical Review Form for Quantitative Studies. If there were differences in the risk of bias scores between the two authors, all authors discussed and reached a consensus. Studies with a high risk of bias were carefully reviewed again, and their inclusion was reconsidered. This collaborative approach helped maintain the accuracy and reliability of the review process.

Results

A comprehensive search of the literature in electronic databases resulted in the identification of 4,158 articles. After removing 142 duplicates, 4,016 records were retained for title and abstract review. Among these, 4,006 articles were excluded for reasons such as not including children with ASD aged 3-18 years, not focusing on the relationship between sensory processing and social functioning in children with ASD, and being review articles. Consequently, 10 full-text articles were evaluated for eligibility, with 8 studies fulfilling the inclusion criteria. Two studies were excluded after the full-text review: one study did not have a separate statistical analysis to evaluate the relationship between sensory processing and social functioning, as typically developing children and children with ASD were combined in the statistical analysis. Another study included children with ASD aged 3-18 years but also covered a more comprehensive age range of up to 54 years, with no separate analysis within the age group of 3-18 years. The PRISMA diagram visually represents the review process (Figure 1).

All eight studies were critically appraised using the McMaster Critical Review Form for Quantitative Studies. Four studies yielded a score of 13, two scored 12, while the remaining two scored 11, denoting "very good" and "good" methodological quality, respectively. The critical appraisal is summarized in Table 1.

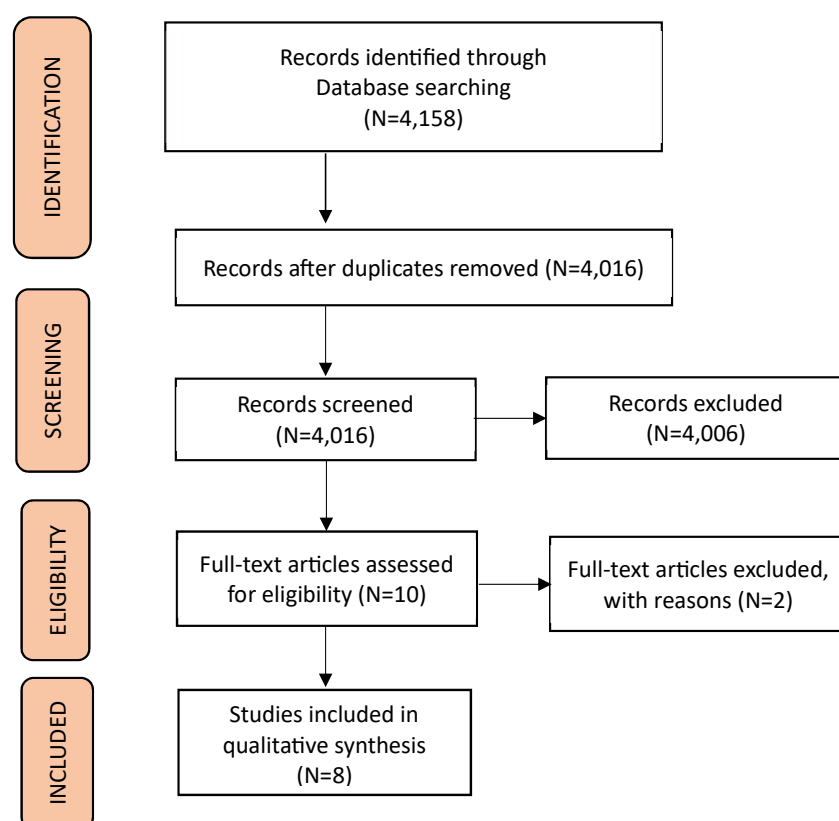


Figure 1. PRISMA flow diagram.

Table 1. Critical appraisal of included studies- McMaster Critical Review Form for Quantitative Studies.

No.	Items	Zhai et al. ²²	Kilroy et al. ²⁵	Pickard et al. ²⁶	Kojovic et al. ²⁷	Dakopoulos & Jahromi ²⁹	Linke et al. ²³	Miguel et al. ³⁰	Matsushima & Kato ²⁴
1	Purpose	1	1	1	1	1	1	1	1
2	Review of Literature	1	1	1	1	1	1	1	1
3	Study design	1	1	1	1	1	1	1	1
4	Biases	0	0	0	0	0	0	0	0
5	Sample	1	1	1	1	1	1	1	1
6	Sample size justification	0	0	0	0	0	0	0	0
7	Informed consent	1	1	1	1	1	1	1	1
8	Validity of outcome measures	1	1	0	0	0	1	1	1
9	Reliability of outcome measures	1	1	0	0	1	1	1	1
10	Intervention	NA	NA	NA	NA	NA	NA	NA	NA
11	Statistical reporting of results	1	1	1	1	1	1	1	1
12	Statistical analysis	1	1	1	1	1	1	1	1
13	Clinical importance	1	1	1	1	1	1	1	1
14	Conclusions	1	1	1	1	1	1	1	1
15	Clinical implications	1	1	1	1	1	1	1	1
16	Study limitations	0	1	1	1	1	1	1	1
Total Score		12	13	11	11	12	13	13	13

Measurement of Social Participation

In 3 studies, social participation was measured using the Social Responsiveness Scale,²²⁻²⁴ whereas 3 studies used the 2nd Edition of the Social Responsiveness Scale.²⁵⁻²⁷ The Social Responsiveness Scale is the most reliable measure for social behavior related to ASD based on the Diagnostic and Statistical Manual of Mental Disorders. It is a 65-item rating scale completed by the child's teacher or parents. The assessment tool demonstrates strong internal consistency, test-retest reliability, well-established content validity, and concurrent, construct and predictive validity.²⁸ In 1 study, social function is measured through social items embedded within the Child Behavior Scale.²⁹ Pickard *et al.* investigated the role of social anxiety in sensory processing using Liebowitz Social Anxiety Scale.²⁶ The Social function domain of Autism Diagnostic Interview-Revised, the Social interaction domain of Autism Diagnostic Schedule, the Social Communication Questionnaire- Lifetime, and the Socialization domain of Vineland Adaptive Behavior Scale- 2nd Edition are the other self-report or parent questionnaires used to measure social function in the included studies of the systematic review.

Two studies employed objective measures: Kojovic *et al.* used an eye-tracking paradigm in which children passively observe three social scenes, each re-enacting everyday situations, allowing for the quantification of visual exploration dynamics and estimation of gaze patterns during naturalistic social interactions.²⁷ Meanwhile, Dakopolos & Jahromi used an Adapted Early Social Communication Scale in which the experimenter and the child interact using various toys. These interactions are then video recorded and coded to evaluate joint attention.²⁹

Measurement of sensory processing

In two studies, sensory processing was measured with the Short Sensory Profile,^{22,27} and three studies used the long form of the family of sensory profile assessments such as original Sensory Profile, Child Sensory Profile-2,

and Adolescent/Adult Sensory Profile.^{26,23,30} The Sensory Profile family of assessments is the most reliable and valid caregiver's questionnaire used to gather information on how an individual responds to various sensory stimuli within different contexts.^{31,32} In one study, the Sensory Experience Questionnaire was used to evaluate sensory processing. The Sensory Experience Questionnaire is a caregiver questionnaire that helps to outline the sensory processing difficulties in children with ASD, both in social and non-social contexts.³³ Another study conducted in Japan utilized the Japanese Sensory Inventory-Revised.²⁴ Finally, only one study investigated the influence of praxis on social participation using the Florida Apraxia Battery (modified for children) and Postural Praxis domain from the Sensory Integration and Praxis Test.²⁵

Relation between social participation and sensory processing in children with autism spectrum disorder

Literature suggests a definite relationship between social participation difficulties and atypical SP in children with ASD. Seven studies revealed a statistically significant association between social participation and SP. The eight studies are summarized in Table 2.

Zhai *et al.* suggest a strong association between SP and social dimensions, indicating that children with SP challenges may struggle to engage socially. Additionally, the study found that sensory processing predicts social functioning in individuals with ASD.²² According to Kilroy *et al.* there is no relationship between praxis and social function.²⁵ Kojovic *et al.* highlighted the significant influence of SP difficulties on the overall processing of social information in children with autism.²⁷ This indicates that abnormalities in SP might significantly interfere with the child's capabilities to understand, interpret, and respond to social cues effectively, thereby increasing the social challenges commonly associated with ASD. The impact of SP on social participation in children with ASD is discussed further through two different lenses: sensory threshold and sensory system.

Table 2. Synthesis of studies examining sensory processing and social participation in children with Autism Spectrum Disorder (ASD).

Studies	Aim	Study Design and Sample Characteristics	Assessments used	Findings
Zhai et al. ²²	To investigate the relationship between SP and social functioning in children diagnosed with ASD.	Study design: Cross-sectional design Sample: • The study included 266 children diagnosed with ASD and 223 healthy children. • The average age of children with autism was 5.31 ± 0.102 years, while the control group had an average age of 5.32 ± 0.115 years. • A psychiatrist and clinical psychologist confirmed the diagnosis using the DSM-5 criteria.	Sensory Processing: • Short Sensory Profile (SSP) Social Participation: • Social Responsiveness Scale • Social function domain of Autism Diagnostic Interview-Revised • Social interaction domain of Autism Diagnostic Schedule	• Spearman correlation analysis revealed inverse associations between the scores of gustatory/olfactory and motor sensitivities from SSP and the social function scores derived from the Autism Diagnostic Interview-Revised. • Additionally, a negative correlation was found between the auditory filtering score and the social interaction score obtained from the Autism Diagnostic Schedule. • The total score of the Social Responsiveness Scale correlated with the tactile, gustation/olfaction, hypo-sensitivity/sensory seeking, auditory filtering, low Strength, and vision/auditory domains of SSP, as well as the total score of SSP. • Also, the study found that sensory characteristics have the potential to act as good predictors of social functioning among children with ASD.
Kilroy et al. ²⁵	To investigate the relationship between social, praxis, and motor skills of children with ASD, Developmental Coordination Disorder, and typically developing individuals.	Study design: Cross-sectional design Sample: • The study included a total of 96 children aged between 8 and 17 years, comprising 35 typically developing children, 33 children diagnosed with ASD, and 28 children diagnosed with Developmental Coordination Disorder.	Sensory Processing: • Florida Apraxia Battery, modified for children. • Postural Praxis domain from the Sensory Integration and Praxis Test Social Participation • Social Responsiveness Scale-2	• The study concluded that there were no significant correlations between the Social Responsiveness Scale-2 and praxis measures (Florida Apraxia Battery and Postural Praxis domain from the Sensory Integration and Praxis Test).

Table 2. Synthesis of studies examining sensory processing and social participation in children with Autism Spectrum Disorder (ASD). (continued)

Studies	Aim	Study Design and Sample Characteristics	Assessments used	Findings
Pickard et al. ²⁶	To investigate the association between cognitive, emotional, SP, and social anxiety in individuals with autism and neurotypical children.	Study design: Cross-sectional design Sample: - A total of 61 autistic individuals and 62 neurotypical individuals aged between 11 and 18 years were recruited for the study. - In the autistic group, 46 (75%) received a diagnosis of autism and 15 (25%) received a diagnosis of Asperger's Syndrome.	Sensory Processing - Adolescent/Adult Sensory Profile - Porges Body Perception Questionnaire (measures interoception) Social Participation - Social Responsiveness Scale- 2 - Liebowitz Social Anxiety Scale - Social Communication Questionnaire- Lifetime	- There was a significant association between the autistic traits (as measured by the Social Responsiveness Scale-2 and the Social Communication Questionnaire - Lifetime) and sensory hypersensitivity in individuals with ASD. - In the autistic group, self-reported social anxiety was significantly associated with increased sensory hypersensitivity. - In children with autism, there was a significant moderate correlation between interoception and social anxiety.
Kojovic et al. ²⁷	To explore the association between SP challenges or differences and social impairments, as well as adaptive functioning, in young children diagnosed with ASD	Study design: Cross-sectional design Sample: - The study included 64 children diagnosed with ASD, aged 3.0 to 5.9 years, and 36 typically developing children, aged 3.1 to 5.9 years. - All children with ASD were clinically diagnosed using DSM-5 criteria.	Sensory Processing - Short Sensory Profile Social Participation - Social Responsiveness Scale-2 - Socialization domain of Vineland Adaptive Behavior Scale-2nd edition. - Eye-Tracking Paradigm (objective measure of social attention extracted from the eye-tracking)	- The Short Sensory Profile was negatively correlated with the Social Responsiveness Scale-2 total score and its domain scores in autistic children. Additionally, the correlation analysis of subsections of the Short Sensory Profile-2 and the total score of the Social Responsiveness Scale-2 revealed the strongest correlation between tactile (P < 0.0010), under-responsiveness /sensory seeking (p < 0.0010), auditory filtering (p<0.0010), and social impairment. - A significant correlation was found between the total scores of the Short Sensory Profile and the socialization domain of the Vineland Adaptive Behavior Scale-2nd edition. Additionally, the auditory-filtering subsection of the Short Sensory Profile strongly correlated with socialization (p < 0.0018). - Children with ASD and sensory issues significantly impact the processing of social information more than age-matched typically developing peers.

Table 2. Synthesis of studies examining sensory processing and social participation in children with Autism Spectrum Disorder (ASD). (continued)

Studies	Aim	Study Design and Sample Characteristics	Assessments used	Findings
Dakopoulos & Jahromi ²⁹	The objective of this study was to assess SP patterns, social competence, and joint attention in children diagnosed with ASD	Study design: Cross-sectional design Sample: - The study comprised 18 children diagnosed with autism and 20 typically developing children, aged between 2.6 and 6 years. - All children with ASD were clinically diagnosed by developmental pediatricians or clinical psychologists, following the DSM criteria.	Sensory Processing - Sensory Experience Questionnaire Social Participation - Child Behavior Scale - Adapted version of Early Social Communication Scale (measure joint attention)	Partial Pearson correlation analysis revealed a significant correlation between sensory hyperresponsiveness, sensory hyposensitiveness, and social competence in children with autism. Also, the study found that children with atypical sensory responses have problems with joint attention.
Linke et al. ²³	To investigate the interhemispheric and thalamocortical connectivity within the auditory network are linked to atypical sound processing and related to social cognition and communication deficits.	Study design: Cross-sectional design Sample: - The study included 40 children diagnosed with autism and 38 typically developing children, all aged between 8 and 17 years. - Autism Diagnostic Interview-Revised was used to confirm the diagnosis of autism.	Sensory Processing - Sensory Profile Social Participation - Social Responsiveness Scale	The severity of social symptoms in children with ASD was linked to auditory abnormalities measured by the sensory profile. Furthermore, the study found that reduced interhemispheric connectivity between the left and right auditory regions was associated with more significant deficits in auditory sensory processing in children with ASD.
Miguel et al. ³⁰	To investigate whether tactile processing predicts social difficulties in children diagnosed with ASD.	Study design: Cross-sectional design Sample: - The study included 44 children diagnosed with ASD, aged between 6 and 14 years. - All children received the diagnosis from a psychiatrist and met the criteria for ASD.	Sensory Processing - Child Sensory profile-2 Social Participation - Social Communication Questionnaire	The study found that tactile hypersensitivity and hyposensitivity were the most significant indicators of social challenges in children with ASD. While tactile seeking did not show a strong predictive relationship with social problems in children with ASD.

Table 2. Synthesis of studies examining sensory processing and social participation in children with Autism Spectrum Disorder (ASD). (continued)

Studies	Aim	Study Design and Sample Characteristics	Assessments used	Findings
Matushima & Kato ²⁴	To examine the relationship between sensory processing disorder and social interaction deficits in Japanese children with ASD aged 4 to 6 years	Study design: Cross-sectional design Sample: • The study involved 42 children diagnosed with ASD and an equal number of typically developing children, aged between 2.6 and 6 years. • All children with ASD received diagnoses from psychiatrists and confirmed based on the standard diagnostic criteria of the DSM-4.	Sensory Processing • Japanese Sensory Inventory- Revised Social Participation • Social Responsiveness Scale	• Spearman's rank correlation analysis showed a significant association between the Social Responsiveness Scale and the Japanese Sensory Inventory-Revised, along with its various domains, including vestibular, tactile, proprioception, auditory, visual, and taste.

1. Based on the sensory threshold

Pickard *et al.* (2020) reported that ASD children with sensory hypersensitivity are more prone to experience social anxiety, limiting their ability to engage in social interactions.²⁶ Kojovic *et al.* found that SUR and SS behaviors were strongly linked to challenges in motivation to interact with each other, which include difficulties in initiating and maintaining social interactions or feeling anxious in social contexts.²⁷ Dakopolos & Jahromi found that autistic children who are highly responsive to sensory input tend to face more exclusion from peers and exhibit increased hyperactivity and distractibility. Conversely, ASD children who are less sensitive to sensory stimuli show higher levels of aggression towards peers, increased anxiety, and fearfulness, as well as decreased prosocial behavior, all of which contribute to more significant difficulties in establishing and maintaining positive social relationships.²⁹

2. Based on the sensory systems

Kojovic *et al.* highlighted the significant role of auditory filtering difficulties in autistic children, especially concerning social communication and motivation.²⁷ Also, Linke *et al.* suggested a significant connection between atypical auditory processing and social problems in children with autism.²³ Interestingly, Pickard *et al.* found a link between interoceptive sensibility and social anxiety in children with autism.²⁶ Miguel *et al.* reported that tactile over-responsivity and under-responsivity predict social problems in children with ASD, but not tactile-seeking behavior.³⁰ Matsushima & Kato found that vestibular, tactile, proprioceptive, auditory, and visual processing are strongly associated with social interaction problems in ASD children aged four to six years.²⁴

Discussion

Literature suggests that SP helps children with ASD interpret social cues, regulate emotions, communicate effectively, engage with peers, navigate social settings, and facilitate initiation and maintenance of meaningful relationships.^{22-27,29,30} Therefore, SP abnormalities in autistic children act as barriers to effective social participation, limiting their ability to connect with peers and navigate social environments.

Previous studies report that SP dysfunction in children with ASD includes SOR, SUR, and SS. Children under-responsive to sensory input may appear aloof or disinterested in social situations because they fail to notice or respond to social cues appropriately.²⁷ On the other hand, children who seek sensory input might engage in behaviors aimed at intensifying sensory experiences across various modalities. This leads to socially unacceptable behavior, including constant movement, jumping, crashing, impulsivity, restlessness, and overexpression of affection, which interfere with social interactions and relationships.^{6,27} Individuals with sensory over-responsivity may avoid situations that trigger sensory discomfort, such as crowded places or noisy environments. Even when they participate, sensory distractions can hinder their

engagement, making it difficult to focus on interactions or follow social cues. Moreover, constant exposure to aversive sensory stimuli can lead to increased social anxiety, resulting in withdrawal or avoidance behaviors, which further impact social participation.^{26,29}

Studies have reported various specific sensory domain differences that influence social participation, such as movement, auditory filtering, tactile sensitivity, taste and smell sensitivity, visual/auditory sensitivity, and proprioceptive processing.^{22-24,27} According to Linke *et al.*, children diagnosed with ASD showed reduced connectivity within their brains' left and right auditory cortices. This lack of interhemispheric connections resulted in impairments in auditory sensory processing, which immediately affected their social functioning.²³ Children with ASD and auditory processing difficulties may have the inability to extract relevant sounds or filter out irrelevant sounds and process appropriate information from the environment.²²

Emotional recognition during social interaction relies on intact audio-visual processing. Emotional recognition involves the comprehension of facial expressions and emotional rhythms. Facial expressions convey emotions like happiness or sadness, while emotional rhythms include vocal tone and pitch changes. Integrating visual and auditory cues allows for accurate interpretation of others' emotions. Therefore, impairments in audio-visual processing can hinder emotional recognition, affecting social interactions.²² Also, children with atypical visual processing experience social challenges due to difficulties in learning social behaviors through visual cues, imitation, or feedback.^{34,27}

Tactile processing holds significant importance in the social functions of children with ASD. This is underscored by previous studies suggesting that "skin as a social organ" and social touch facilitate the development and neural connectivity of brain areas associated with social cognition.^{35,36} Additionally, atypical tactile processing in children with ASD is associated with altered gamma-aminobutyric acid (GABA) levels.³⁷ Studies also found that a lack of social touch due to atypical tactile processing may lead to an increased risk of mental health problems.³⁰ Moreover, disruptions in the neural mechanisms that process affective (pleasant) touch have been found in individuals with ASD. These disruptions can further exacerbate difficulties in social relationships.³⁰ Challenges in processing vestibular and proprioceptive information can disrupt regulating arousal levels, body posture maintenance, and movement coordination during social interactions. This can result in avoiding physical contact, displaying unusual body movements, or experiencing discomfort in crowded or unpredictable environments. The cerebellum is essential for processing vestibular and proprioceptive information, and its interaction with other brain regions is critical for social cognition and interaction. Therefore, it is evident that atypical information processing in the cerebellum leads to problems in social participation.³⁴ The underlying mechanism of the relationship between SP and social participation is diverse and multifaceted.³⁴

Parent-reported measures rather than objective

measures dominate measures for assessing SP in children with ASD. The subjective sensory processing measures include the Sensory Profile, Sensory Profile 2, Adolescent/Adult Sensory Profile, Short Sensory Profile, and Sensory Experience Questionnaire. While these instruments generally demonstrate acceptable reliability and validity, they must be cautious when applied in diverse contexts or with different demographic groups, as their development and standardization are primarily focused on the US population. Additionally, only one study used the Japanese Sensory Inventory-Revised,²⁴ highlighting the necessity for cultural adaptation and validation when assessing sensory processing across varied populations.

The primary limitations of this systematic review include the use of only three databases and a focus solely on literature published in English. These constraints may have resulted in the exclusion of relevant studies within our review's scope. The exclusion of non-English studies and studies not indexed in the selected databases might result in missing valuable data or findings. This could limit the comprehensiveness of the review by omitting findings from diverse cultural or regional contexts and reducing the generalizability of the conclusions. Furthermore, the studies included in the review vary widely in methodologies, participant characteristics (such as ASD severity, socio-economic status, etc.), outcome measures, and definitions of social participation, which poses challenges in drawing consistent conclusions.

Beyond sensory processing difficulties, several other factors may interfere with the social participation of children with ASD. These factors include communication challenges, such as verbal and non-verbal communication, and behavioral challenges, such as repetitive behaviors and emotional dysregulation.¹⁴⁻¹⁶ Co-occurring conditions, including anxiety and depression, may further influence social interactions, while cognitive differences, such as impairments in executive functioning, can also affect social participation.¹⁷ Additionally, environmental barriers, such as inadequate support from social settings, social stigma, bullying, or lack of opportunities for social engagement, can also contribute to social problems in children with ASD.³⁸

This systematic review will enhance the understanding of how SP impacts social participation in children with ASD, thereby improving assessment protocols for both SP issues and social functions in children with ASD. Additionally, it will aid in the development of tailored interventions and support strategies to manage social participation difficulties in children with ASD.

Conclusion

This systematic review concludes that the difficulty in SP impacts social participation in children with ASD. Therefore, SP is a foundation for successful social function across various contexts and enhances overall social well-being. However, the nature of sensory processing challenges and the specific sensory systems affected are diverse and inconsistent. The majority of included studies were cross-sectional or retrospective; therefore, there is

a need for longitudinal research to explain the temporal dynamics of SP and social participation in children with autism. Additionally, more research is needed to thoroughly examine how sensory processing relates to the social involvement, as well as to assess the influence of other factors such as socio-economic status, parent education, cognitive abilities, screen time exposure, and schooling on both typically developing children and those with ASD.

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Conflict of interest

All the authors declare no conflicts of interest

References

- [1] Case-Smith J, O'Brien JC. Occupational Therapy for Children and Adolescents, 6th ed. St. Louis, Missouri: Elsevier; 2015.
- [2] Jahromi LB, Meek SE, Ober-Reynolds S. Emotion regulation in the context of frustration in children with high functioning autism and their typical peers. *J Child Psychol Psychiatry*. 2012; 53: 1250-8. doi: 10.1111/j.1469-7610.2012.02560.x.
- [3] Conner CM, White SW, Scahill L, Mazefsky CA. The role of emotion regulation and core autism symptoms in the experience of anxiety in autism. *Autism*. 2020; 24: 931-940. doi: 10.1177/1362361320904217.
- [4] Boyd BA, McDonough SG, Bodfish JW. Evidence-based behavioral interventions for repetitive behaviors in autism. *J Autism Dev Disord*. 2012; 42: 1236-48. doi: 10.1007/s10803-011-1284-z.
- [5] Chang YC, Quan J, Wood JJ. Effects of Anxiety Disorder Severity on Social Functioning in Children with Autism Spectrum Disorders. *J Dev Phys Disabil*. 2012; 24: 235-45.
- [6] Loh SY, Ee SI, Marret MJ. Sensory processing and its relationship to participation among childhood occupations in children with autism spectrum disorder: exploring the profile of differences. *Int J Dev Disabil*. 2021; 69: 226-237. doi: 10.1080/20473869.2021.1950484.
- [7] Ismael N, Lawson LM, Hartwell J. Relationship Between Sensory Processing and Participation in Daily Occupations for Children With Autism Spectrum Disorder: A Systematic Review of Studies That Used Dunn's Sensory Processing Framework. *Am J Occup Ther*. 2018; 72: 7203205030p1-7203205030p9. doi: 10.5014/ajot.2018.024075.
- [8] Bundy AC, Lane SJ. Sensory Integration Theory and Practice, 3rd ed. Philadelphia, Pennsylvania: F.A.Davis; 2020.
- [9] Tomchek SD, Dunn W. Sensory processing in children with and without autism: a comparative study using the short sensory profile. *Am J Occup Ther*. 2007; 61: 190-200. doi: 10.5014/ajot.61.2.190.
- [10] Miller LJ, Anzalone ME, Lane SJ, Cermak SA, Osten ET. Concept evolution in sensory integration: a proposed

- nosology for diagnosis. *Am J Occup Ther.* 2007; 61: 135-40. doi: 10.5014/ajot.61.2.135.
- [11] Lin LY. Activity Participation and Sensory Processing Patterns of Preschool-Age Children With Autism Spectrum Disorder. *Am J Occup Ther.* 2020; 74: 7406345010p1-7406345010p7. doi: 10.5014ajot.2020.039297.
- [12] Bedell G, Coster W, Law M, Liljenquist K, Kao YC, Teplicky R, et al. Community participation, supports, and barriers of school-age children with and without disabilities. *Arch Phys Med Rehabil.* 2013; 94: 315-23. doi: 10.1016/j.apmr.2012.09.024.
- [13] Darling-Churchill KE, Lippman L. Early childhood social and emotional development: Advancing the field of measurement. *J Appl Dev Psychol.* 2016; 45: 1-7. doi: 10.1016/j.appdev.2016.02.002.
- [14] Kasari C, Locke J, Gulsrud A, Rotheram-Fuller E. Social networks and friendships at school: comparing children with and without ASD. *J Autism Dev Disord.* 2011; 41: 533-44. doi: 10.1007/s10803-010-1076-x.
- [15] Kuhaneck HM, Britner PA. A preliminary investigation of the relationship between sensory processing and social play in autism spectrum disorder. *OTJR: Occupation, Participation and Health.* 2013; 33: 159-67. doi: 10.3928/15394492-20130614-04.
- [16] Cosbey J, Johnston SS, Dunn ML, Bauman M. Playground Behaviors of Children with and without Sensory Processing Disorders. *OTJR: Occupational Therapy Journal of Research.* 2012; 32: 39-47. doi:10.3928/15394492-20110930-01.
- [17] Cosbey J, Johnston SS, Dunn ML. Sensory processing disorders and social participation. *Am J Occup Ther.* 2010; 64: 462-73. doi: 10.5014/ajot.2010.09076.
- [18] Tavassoli T, Miller LJ, Schoen SA, Jo Brout J, Sullivan J, Baron-Cohen S. Sensory reactivity, empathizing and systemizing in autism spectrum conditions and sensory processing disorder. *Dev Cogn Neurosci.* 2018; 29: 72-77. doi: 10.1016/j.dcn.2017.05.005.
- [19] Reynolds S, Bendixen RM, Lawrence T, Lane S. A pilot study examining activity participation, sensory responsiveness, and competence in children with high functioning autism spectrum disorder. *J Autism Dev Disord.* 2011; 41: 1496-506. doi: 10.1007/s10803-010-1173-x.
- [20] Law M, Stewart D, Letts L, Pollock N, Bosch J, Westmorland M. Critical review form-Qualitative and quantitative studies. Hamilton, Canada: McMaster University. 1998.
- [21] Wells C, Kolt GS, Marshall P, Hill B, Bialocerkowski A. The effectiveness of Pilates exercise in people with chronic low back pain: a systematic review. *PLoS One.* 2014; 9: e100402. doi: 10.1371/journal.pone.0100402.
- [22] Zhai J, Li X, Zhou Y, Fan L, Xia W, Wang X, et al. Correlation and predictive ability of sensory characteristics and social interaction in children with autism spectrum disorder. *Front Psychiatry.* 2023; 14: 1056051. doi: 10.3389/fpsy.2023.1056051.
- [23] Linke AC, Jao Keehn RJ, Pueschel EB, Fishman I, Muller RA. Children with ASD show links between aberrant sound processing, social symptoms, and atypical auditory interhemispheric and thalamocortical functional connectivity. *Dev Cogn Neurosci.* 2018; 29: 117-126. doi: 10.1016/j.dcn.2017.01.007.
- [24] Matsushima K, Kato T. Social interaction and atypical sensory processing in children with autism spectrum disorders. *Hong Kong J Occup Ther.* 2013; 23: 89-96. doi: 10.1016/j.hkjot.2013.11.003
- [25] Kilroy E, Ring P, Hossain A, Nalbach A, Butera C, Harrison L, et al. Motor performance, praxis, and social skills in autism spectrum disorder and developmental coordination disorder. *Autism Res.* 2022; 15: 1649-64. doi: 10.1002/aur.2774.
- [26] Pickard H, Hirsch C, Simonoff E, Happe F. Exploring the cognitive, emotional and sensory correlates of social anxiety in autistic and neurotypical adolescents. *J Child Psychol Psychiatry.* 2020; 61: 1317-27. doi: 10.1111/jcpp.13214.
- [27] Kojovic N, Ben Hadid L, Franchini M, Schaer M. Sensory Processing Issues and Their Association with Social Difficulties in Children with Autism Spectrum Disorders. *J Clin Med.* 2019; 8: 1508. doi: 10.3390/jcm8101508.
- [28] Bruni TP. Test review: Social Responsiveness Scale-second edition (SRS-2). *J Psychoeduc Assess.* 2014; 32: 365-9. doi: 10.1177/0734282913517525
- [29] Dakopoulos AJ, Jahromi LB. Differences in sensory responses among children with autism spectrum disorder and typical development: Links to joint attention and social competence. *Infant Child Dev.* 2018; 28: e2117. doi: 10.1002/icd.2117
- [30] Miguel HO, Sampaio A, Martínez-Regueiro R, Gomez-Guerrero L, Lopez-Doriga CG, Gomez S, et al. Touch Processing and Social Behavior in ASD. *J Autism Dev Disord.* 2017; 47: 2425-33. doi: 10.1007/s10803-017-3163-8.
- [31] Dunn, W. Sensory profile. San Antonio, Texas: Psychological Corporation; 1999.
- [32] Dunn, W. Sensory profile, 2nd ed. San Antonio, Texas: Psychological Corporation; 2014.
- [33] Baranek GT, David FJ, Poe MD, Stone WL, Watson LR. Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and typical development. *J Child Psychol Psychiatry.* 2006; 47: 591-601. doi: 10.1111/j.1469-7610.2005.01546.x.
- [34] Thyne MD, Bednarz HM, Herringshaw AJ, Sartin EB, Kana RK. The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Dev Cogn Neurosci.* 2018; 29: 151-67. doi: 10.1016/j.dcn.2017.04.010.
- [35] Gordon I, Voos AC, Bennett RH, Bolling DZ, Pelphrey KA, Kaiser MD. Brain mechanisms for processing affective touch. *Hum Brain Mapp.* 2013; 34: 914-22. doi: 10.1002/hbm.21480.
- [36] Björnsdotter M, Gordon I, Pelphrey KA, Olausson H,

- Kaiser MD. Development of brain mechanisms for processing affective touch. *Front Behav Neurosci.* 2014; 8: 24. doi: 10.3389/fnbeh.2014.00024.
- [37] Puts NAJ, Wodka EL, Harris AD, Crocetti D, Tommerdahl M, Mostofsky SH, et al. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Res.* 2017; 10: 608-19. doi: 10.1002/aur.1691.
- [38] Hoover DW. The Effects of Psychological Trauma on Children with Autism Spectrum Disorders: a Research Review. *Rev J Autism Dev Disord.* 2015; 2: 287-99. Doi: 10.1007/s40489-015-0052-y

Prevalence and antimicrobial resistance of *Salmonella* isolated from pork in the Northern part of Thailand

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ABSTRACT

Background: *Salmonella* is one of the most common foodborne bacteria frequently isolated from pork. It poses significant public health risks due to its potential to harbor antimicrobial resistance (AMR) genes. The emergence and spread of multidrug-resistant (MDR) *Salmonella* strains are of particular concern as these can be transferred to humans through food or contaminated environments.

Objective: To determine *Salmonella*'s prevalence and antimicrobial resistance determinants from pork at retail markets in the Northern part of Thailand.

Materials and methods: *Salmonella* was isolated and identified from 173 pork samples. The isolates were serotyped using the slide agglutination test with somatic (O) and flagellar (H) antigens, and tested for antimicrobial susceptibility using 23 different antimicrobials using the disc diffusion method. By polymerase chain reaction (PCR), the extended-spectrum β -lactamases (ESBL) genes (bla_{TEM} , bla_{SHV} , $bla_{CTX-M-1'}$, $bla_{CTX-M-2'}$, $bla_{CTX-M-8/25}$ and $bla_{CTX-M-9}$), quinolone-resistance determining region (QRDR) including *gyrA*, *gyrB*, *parC* and *parE*, plasmid-mediated quinolone resistance (PMQR) determinants including *qnrA*, *qnrB*, *qnrD*, *qnrS*, and *aac(6')-Ib-cr* were determined.

Results: In this study, 98.8% of the samples were identified as *Salmonella*. Among these, 72.5% of isolates showed resistance to at least 1 antimicrobial agent and 48.5% were MDR. Ampicillin/tetracycline/trimethoprim-sulfamethoxazole (AMP/TE/SXT) was the most common phenotypic resistance pattern. The results revealed that 4 ESBL genes (bla_{TEM} , $bla_{CTX-M-1'}$, $bla_{CTX-M-2'}$ and $bla_{CTX-M-9}$) were detected in 3 isolates- identified as ESBL producers. Moreover, all 9 quinolone-mediated resistance determinants were observed in quinolone resistance isolates.

Conclusion: The results demonstrated that most MDR isolates harbored quinolone resistance determinants. We report the distribution of MDR in *Salmonella* strains isolated from pork and the correlation between the phenotypic and the genotypic susceptibility. These findings raise great concern about the spread of resistant *Salmonella* strains in the Northern part of Thailand.

Introduction

Antimicrobial-resistant (AMR) bacteria have emerged as a significant public health concern worldwide. This issue is particularly pronounced in zoonotic foodborne infections, where the misuse and overuse of antimicrobials in human and veterinary medicine have accelerated the spread of resistance.¹ Antimicrobials are commonly employed to prevent and treat diseases in pork production systems.² In developing countries, particularly in South and Southeast Asia, including Thailand, the rise of large-scale farming systems has led to an increased use of

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antimicrobials, contributing to the proliferation of AMR in animals.³

Salmonella is among the most prevalent foodborne bacteria, capable of spreading to humans through contaminated food. Recent studies have reported the presence of *Salmonella* isolated from pork sold in local markets across various provinces in Thailand, including Sa Kaeo, Nong Khai, Bangkok, Chiang Mai, and Lamphun.⁴⁻⁸ These studies have revealed a high incidence of multidrug-resistant (MDR) *Salmonella* strains. Furthermore, a study has indicated that AMR pathogens and genes can be transmitted from animals to humans through the food chain or contaminated environments.³

Cephalosporins and fluoroquinolones are critical antimicrobials used in the treatment of diseases in both humans and animals. In recent years, resistance to β -lactams including penicillins, carbapenems, cephalosporins, and monobactams has become increasingly common, giving rise to extended-spectrum β -lactamase (ESBL)-producing bacteria that can spread to humans through food.⁹ Additionally, fluoroquinolone resistance has risen due to chromosomal mutations in the quinolone-resistance-determining region (QRDR), leading to plasmid-mediated quinolone resistance (PMQR).¹⁰ These resistance mechanisms can be co-transmitted, contributing to high rates of AMR across both antimicrobial classes.¹¹ Resistance to crucially necessary medications cephalosporins and fluoroquinolones might increase human salmonellosis's severity, morbidity, and mortality, necessitating last-line antimicrobial agents (e.g., carbapenems). Furthermore, the World Health Organization has identified Fluoroquinolone-resistant *Salmonella* as a pathogen for whom novel antibiotic research and development are urgently needed.¹²

The emergence and spread of MDR strains resistant to fluoroquinolones and cephalosporins are of grave concern, especially given the frequent contamination of pork with AMR *Salmonella*. Pigs are recognized as significant reservoirs of *Salmonella*, further complicating the issue. Previous studies in Thailand have examined *Salmonella* prevalence in other regions; few have focused on the molecular basis of antimicrobial resistance in pork sold at retail markets in Northern Thailand.⁴⁻⁷ However, to our knowledge, few studies were specific to Phayao province.^{8,13,14}

Therefore, this study aims to determine the presence of antimicrobial resistance genes in pork at retail markets in the northern part of Thailand. These findings could emphasize the need for ongoing surveillance and research to address the challenges posed by *Salmonella* in pork products. Knowledge of the prevalence of the AMR gene in *Salmonella* could enhance consumer concern and promote health awareness of appropriate pork consumption.

Materials and methods

Samples collection

Between February and April 2018, 173 pork samples, about 50 gm per sample, were randomly collected from retail pork shops in seven provinces in northern Thailand:

Chiang Rai, Chiang Mai, Nan, Phayao, Phrae, Lampang, and Lamphun. The sample size was calculated based on Yamane (1967). The samples were collected under sterile conditions, stored in a cold box at 4 °C, and transported to the laboratory on the same day for bacterial isolation.¹⁵

Salmonella Isolation, identification, and serotyping

Isolation and identification of *Salmonella* were conducted following the International Organization for Standardization (ISO) 6579-1:1993 standard.¹⁵ Each 25-gm pork sample was pre-enriched by homogenization in 225 mL of Buffered Peptone Water (BPW). Subsequently, 1 mL of the pre-enriched sample was inoculated into Tetrathionate (TT) broth, and 0.1 mL was inoculated into Rappaport-Vassiliadis soy peptone (RVS) broth. Both broths were selectively enriched with *Salmonella* from food, animal feed, water, and other materials. The enriched samples were then plated on Xylose Lysine Deoxycholate (XLD) agar, a selective growth medium. Culturing in all broth and medium in this study was conducted for 18-24 hrs at 37 °C. Typical *Salmonella* colonies were selected and subjected to biochemical testing. All isolates identified as *Salmonella* spp. were serotyped using O- and H- antisera (Clinag, Thailand) according to the Kauffmann-White scheme.¹⁶ A total of 171 *Salmonella* isolates were identified and selected for further investigation.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method following the Clinical and Laboratory Standards Institute (CLSI, 2019) guidelines to assess the antimicrobial resistance of *Salmonella* isolates. The antimicrobials tested included 1.25/23.75 μ g of trimethoprim/sulfamethoxazole, 5 μ g of ciprofloxacin, levofloxacin, gatifloxacin, and ofloxacin, 30 μ g of nalidixic acid, cefepime, cefotaxime, ceftriaxone, ceftazidime, ceftizoxime, tetracycline and chloramphenicol, 10 μ g of ampicillin, aztreonam, ertapenem, imipenem, meropenem, gentamicin, streptomycin, and norfloxacin, 20/10 μ g of amoxicillin/clavulanic acid, and 75 μ g of cefoperazone. *Escherichia coli* ATCC 25922 was used as a quality control strain. *Salmonella* isolate was classified as multidrug-resistant (MDR) if it resisted three or more antimicrobials.¹⁷ Any isolates resistant to one of the following antibiotics, ceftazidime (30 μ g), cefotaxime (30 μ g), or ceftriaxone (30 μ g) were defined as suspected ESBL isolates. Suspected extended-spectrum β -lactamase (ESBL)-producing isolates were confirmed using the combination disk method with cefotaxime (30 μ g) and ceftazidime (30 μ g), both with and without clavulanic acid (10 μ g), following CLSI guidelines. An isolate showing a difference of ≥ 5 mm. between the inhibition zone of the antibiotic disk with and without clavulanic acid was interpreted as an ESBL producer.

DNA extraction and antimicrobial resistance determinant detection

The isolates were cultured overnight on fresh Mueller–Hinton broth at 37°C and then the genomic DNA was

extracted from the isolates using a PureDireX Genomic DNA Isolation Kit (Bio-Helix, Taiwan) according to the manufacturer's instructions and kept at -20°C before used. The presence of ESBL genes and quinolone resistance was screened in the isolated strains to detect resistance determinants. Specifically, the quinolone-resistance determining regions (QRDR) including *gyrA*, *gyrB*, *parE*, and *parC*, as well as plasmid-mediated quinolone resistance (PMQR) determinants such as *qnrA*, *qnrB*, *qnrD*, *qnrS*, and *aac(6')-Ib-cr*, were detected using PCR with specific primers as previously described.¹⁸ Additionally, up to six types of ESBL genes (*bla*_{TEM}, *bla*_{SHV}, *bla*_{CTX-M-1}, *bla*_{CTX-M-2},

*bla*_{CTX-M-8/25}, and *bla*_{CTX-M-9}) were also detected using PCR. The primers and product sizes used in this study are shown in Table 1. For PCR reactions, each reaction mixture 25 µL was prepared, containing 2X PCR Master mix Solution (i-Taq™, Korea), 10 µM for each primer for each set of PCR, and 1 µL of DNA template. The PCR cycling conditions were 2 min at 94°C; 30 cycles of 20 sec at 94°C, 10 sec at 55-61°C and 45 sec at 72°C; with a final extension at 72°C for 5 min. The selected PCR amplicons were sequenced and compared with sequences available in the GenBank nucleotide database (www.ncbi.nlm.nih.gov /BLAST).

Table 1. List of primers used in this study for amplification of antibiotic-resistant genes.

Antimicrobial target	Target gene	Primer sequence (5'-3')	Amplicon size (bp)	Annealing temperature (°C)	References
ESBL	<i>bla</i> _{TEM}	CATTTCCGTGTCGCCCTTATTC CGTTCATCCATAGTTGCCTGAC	800	58	18
	<i>bla</i> _{SHV}	AGCCGCTTGAGCAAATTAAAC ATCCCGCAGATAAATCACCAC	713	58	
	<i>bla</i> _{CTX-M-1}	TTAGGAARTGTGCCGCTGYAA CGATATCGTTGGTGGTRCCATA	688	57	
	<i>bla</i> _{CTX-M-2}	CGTTAACGGCAGCATGAC CGATATCGTTGGTGGTRCCATA	404	57	
	<i>bla</i> _{CTX-M-9}	TCAAGCCTGCCGATCTGGT TGATTCTCGCCGCTGAAG	561	58	
	<i>bla</i> _{CTX-M-8/25}	AACRCRCAGACGCTCTACA TCGAGCCGGAASGTGTATATA	326	55	
QRDR	<i>gyrA</i>	TGGGCAATGACTGGAACA GGTTGTGCGGCGGGATA	431	55	17
	<i>gyrB</i>	ATGAGCGATATGGCAGAGCG GCTGTGATAACGCAGTTTGTCCGG	309	61	
	<i>parC</i>	ATGAGCGATATGGCAGAGCG TGACCGAGTTCGCTTAACAG	413	57	
	<i>parE</i>	ATGCGTGCGGCTAAAAAAGTG TCGTCGCTGTGAGGATCGATAC	290	59	
PMQR	<i>qnrA</i>	ATTTCTACGCCAGGATTG GATCGGCAAAGGTTAGGTCA	516	57	17
	<i>qnrB</i>	GATCGTGAAAGCCAGAAAGG ACGATGCCTGGTAGTTGTCC	469	58	
	<i>qnrD</i>	CGAGATCAATTTACGGGGAATA AACAAGCTGAAGCGCTG	656	58	
	<i>qnrS</i>	ACGACATTCGTCAACTGCAA TAAATTGGCACCTGTAGGC	417	55	
	<i>aac(6')-Ib-cr</i>	TTGCGATGCTCTATGAGTGGCTA CTCGAATGCCTGGCGTGT	482	59	

Note: ESBL: extended-spectrum β-lactamases, QRDR: quinolone resistance determining region, PMQR: plasmid-mediated quinolone resistance, bp: base pair.

Results

Salmonella isolation and serogroups distribution

Salmonella was isolated from 171 out of 173 pork samples, resulting in an isolation rate of 98.8% (Figure 1, Table 2). The isolates were classified into 9 distinct

serogroups, with serogroup C being the most prevalent (50.9%), followed by serogroup E (15.8%), serogroup B (12.9%), serogroup G (7.1%), non A-I serogroups (5.3%), serogroup D (3.5%), serogroup I (3.0%), serogroup A (1.2%), and serogroup F (0.6%).

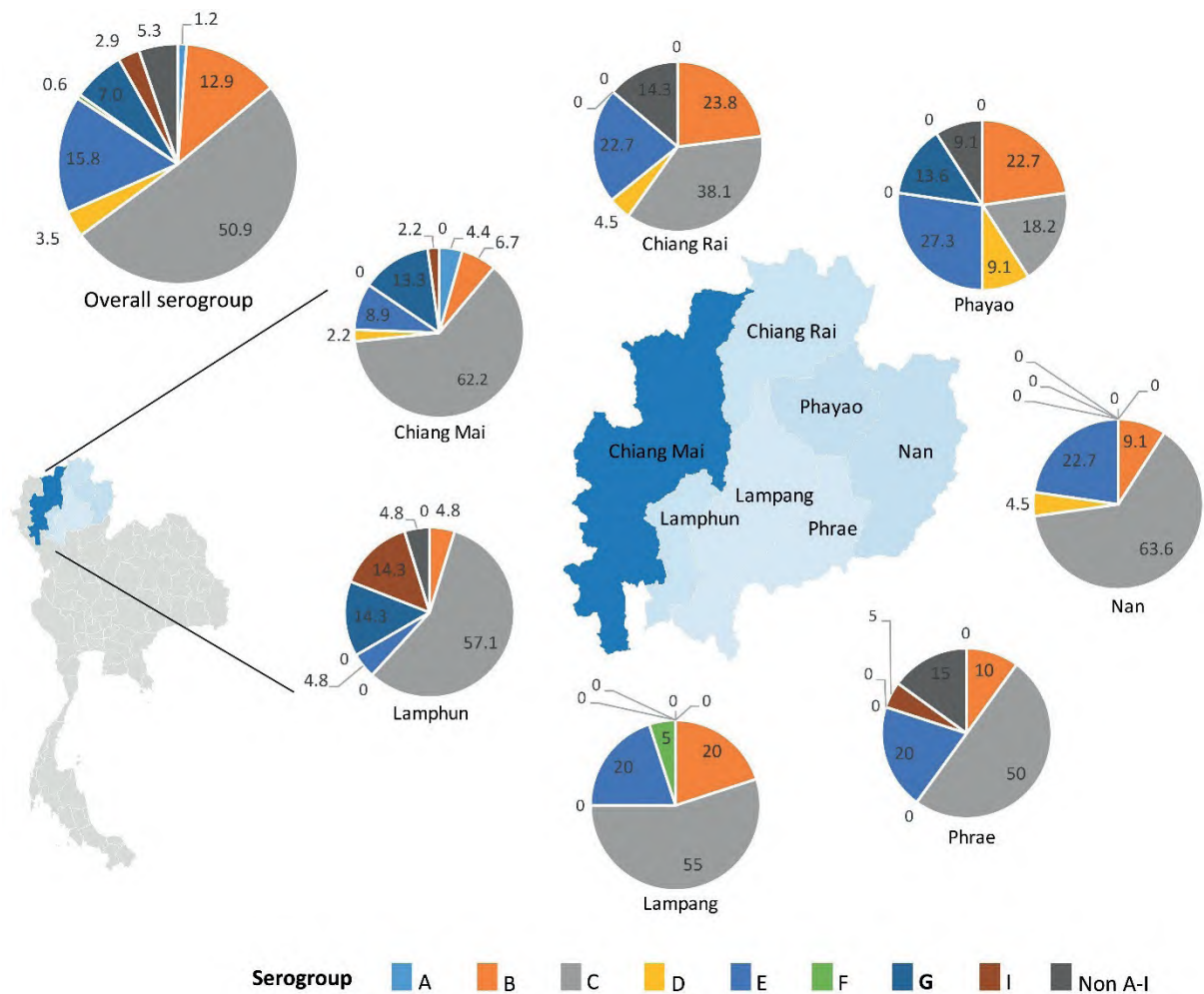


Figure 1. Map of Thailand displaying sampling provinces and serogroup percentages. Serogroup distribution of Salmonella-positive samples isolated from pork sold in retail markets in Northern Thailand (N=171).

Table 2. Serogroup distribution of Salmonella-positive samples isolated from pork and sold in retail markets in Northern Thailand.

Sampling site/ Serogroups	Positive isolates (%)							Total (N=171)
	Chiangmai (N=45)	Chiang Rai (N=21)	Nan (N=22)	Phrae (N=20)	Phayao (N=22)	Lampang (N=20)	Lamphun (N=21)	
A	2 (4.4)	0	0	0	0	0	0	2 (1.2)
B	3 (6.7)	5 (23.8)	2 (9.1)	2 (10.0)	5 (22.7)	4 (20.0)	1 (4.8)	22 (12.9)
C	28 (62.2)	8 (38.1)	14 (63.6)	10 (50.0)	4 (18.2)	11 (55.0)	12 (57.1)	87 (50.9)
D	1 (2.2)	1 (4.5)	1 (4.5)	0	2 (9.1)	0	0	6 (3.5)
E	4 (8.9)	5 (22.7)	5 (22.7)	4 (20.0)	6 (27.3)	4 (20.0)	1 (4.8)	27 (15.8)
F	0	0	0	0	0	1 (5.0)	0	1 (0.6)
G	6 (13.3)	0	0	0	3 (13.6)	0	3 (14.3)	12 (7.0)
I	1 (2.2)	0	0	1 (5.0)	0	0	3 (14.3)	5 (2.9)
Non A-I	0	3 (14.3)	0	3 (15.0)	2 (9.1)	0	1 (4.8)	9 (5.2)

Antimicrobial susceptibility testing

Among the 171 *Salmonella* isolates, 124 (72.5%) demonstrated resistance to at least one antimicrobial agent. Resistance was most observed to ampicillin (55.6%), tetracycline (47.0%), and trimethoprim-sulfamethoxazole (25.0%). Resistance to third- and fourth-generation cephalosporins was identified in 5 isolates (2.9%), while 41 isolates (23.8%) showed resistance to third-generation cephalosporins alone. Additionally, 38 isolates (22.2%) exhibited resistance or intermediate resistance to quinolones and nalidixic acid (NA), of which 3 isolates (1.8%) were confirmed as ESBL producers.

Prevalence of multidrug resistance strains

Multidrug resistance (MDR), defined as resistance to three or more different classes of antimicrobials, was observed in 83 isolates (48.5%). These MDR isolates were distributed across 6 different serogroups and exhibited 48 distinct resistance patterns. Notably, one isolate belonging to serogroup E resisted 15 antimicrobial agents. The most common MDR pattern observed was resistance to ampicillin, tetracycline, and trimethoprim-sulfamethoxazole (AMP/TE/SXT).

Detection of β -lactamase coding genes (ESBL) and quinolone resistance determinants

Quinolone resistance determinants were identified in ten different patterns among the quinolone-resistant isolates including *gyrA*, *gyrA/parC*, *parC/parE*, *gyrA/parC/parE*, *gyrA/parC/qnrB*, *gyrA/parC/parE/qnrA*, *gyrA/parC/parE/qnrS*, *parC/parE/qnrD/qnrS*, *gyrA/parC/parE/qnrA/qnrS*, *gyrA/parC/parE/qnrS/aac(6')-Ib-cr* (Figure 2). The most frequently observed pattern was a combination of *gyrA*, *parC*, and *parE* mutations (*gyrA/parC/parE*),

present in 5.8% of the isolates. Among the QRDR, *parC* (21.0%) was the most common, followed by *gyrA* (20.5%) and *parE* (15.8%). For plasmid-mediated quinolone resistance (PMQR), *qnrS* (8.8%) was the most frequently detected gene. Notably, PMQR genes were not detected in *Salmonella* serogroups A and D. Interestingly, the *gyrA* and *parC* mutations were found among all NA resistance isolates.

In this study, two isolates carried both ESBL genes and quinolone resistance determinants, with these isolates belonging to serogroups C and E. One additional isolate, belonging to serogroup B, harbored ESBL genes. Among the three ESBL-producing isolates, all carried multiple ESBL genes. Two isolates (serogroups C and E) carried *bla_{TEM}* and *bla_{CTX-M-1}* genes, while one isolate (serogroup B) harbored the *bla_{CTX-M-2}* and *bla_{CTX-M-9}* genes. The genotypic distribution of antibiotic-resistance genes detected in this study is detailed in Figure 2. Most of these strains exhibited the AMP/TE/CPZ resistance phenotype, with common resistance determinants to quinolones (Table 3).

Among PCR amplicons detected in this study, 4 types of ESBL genes (*bla_{TEM}*, *bla_{CTX-M-1}*, *bla_{CTX-M-2}*, and *bla_{CTX-M-9}*) and 4 quinolone resistance determinants (*gyrA*, *parC*, *parE*, and *qnrS*) were sequenced and showed more than 98% of nucleotide similarity, excepted *Salmonella* strain with *bla_{CTX-M-2}* gene (78% similarity). The sequences accession number available in the GenBank nucleotide database were used as reference and compared with our PCR amplicons sequences including FJ873740.1 (*bla_{TEM}*), AB672504.1 (*bla_{CTX-M-1}*), LC229068.1 (*bla_{CTX-M-2}*), MF797877.1 (*bla_{CTX-M-9}*), MH933950.1 (*gyrA*), PP175516.1 (*parC*), PP179238.1 (*parE*), and NG_050543.1 (*qnrS*). The sequence alignment against the references is shown in Figure 3.

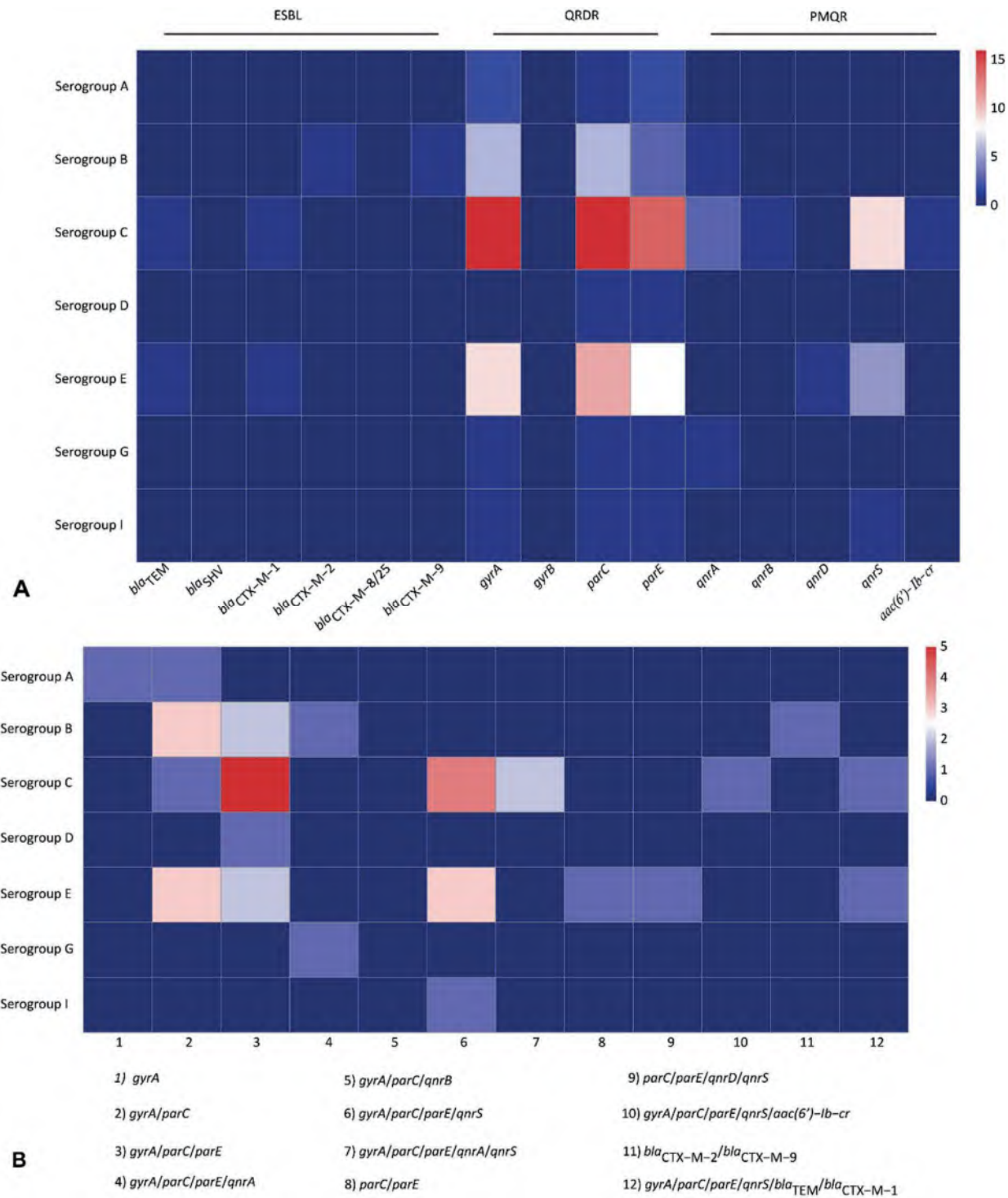
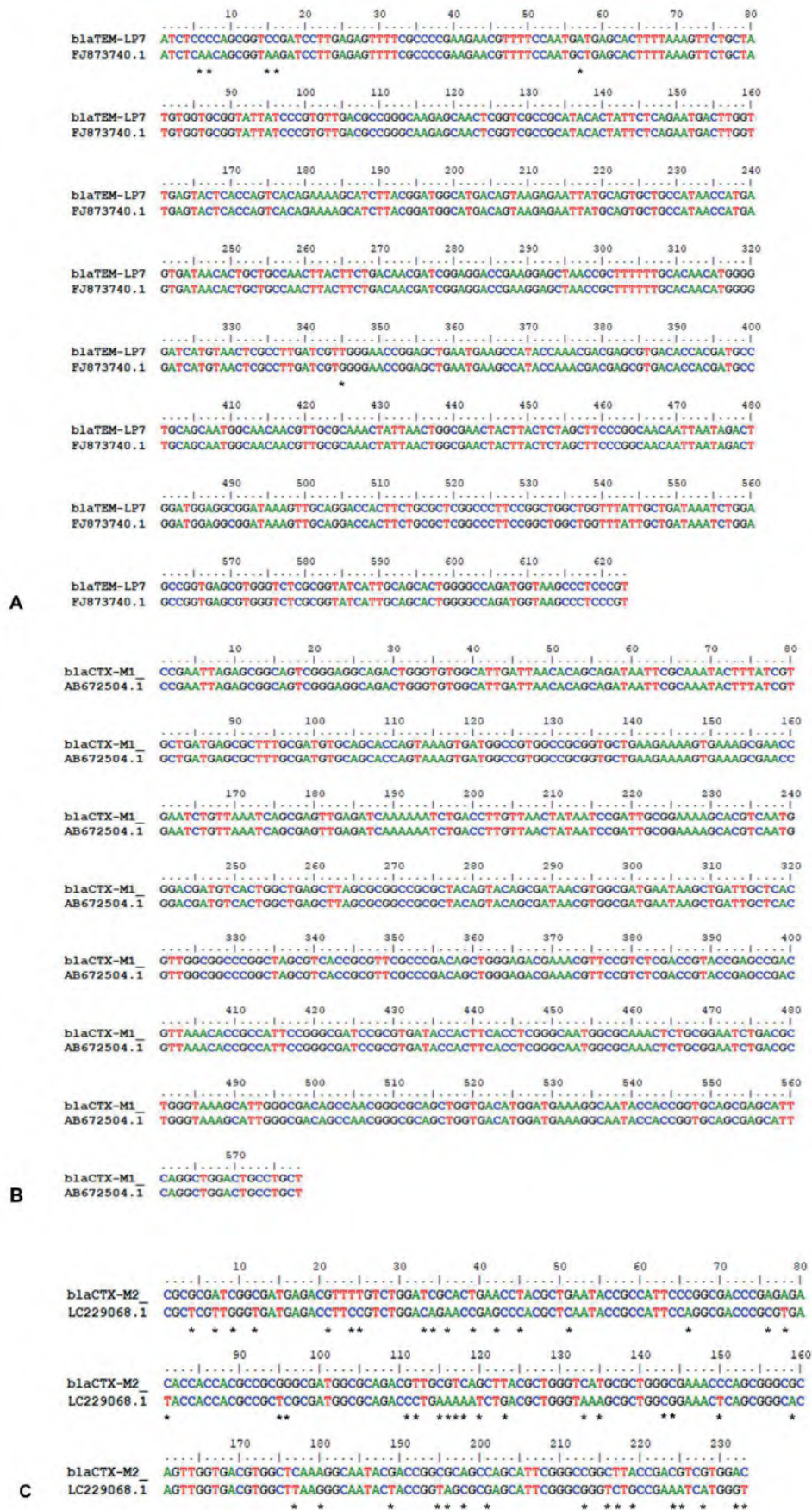


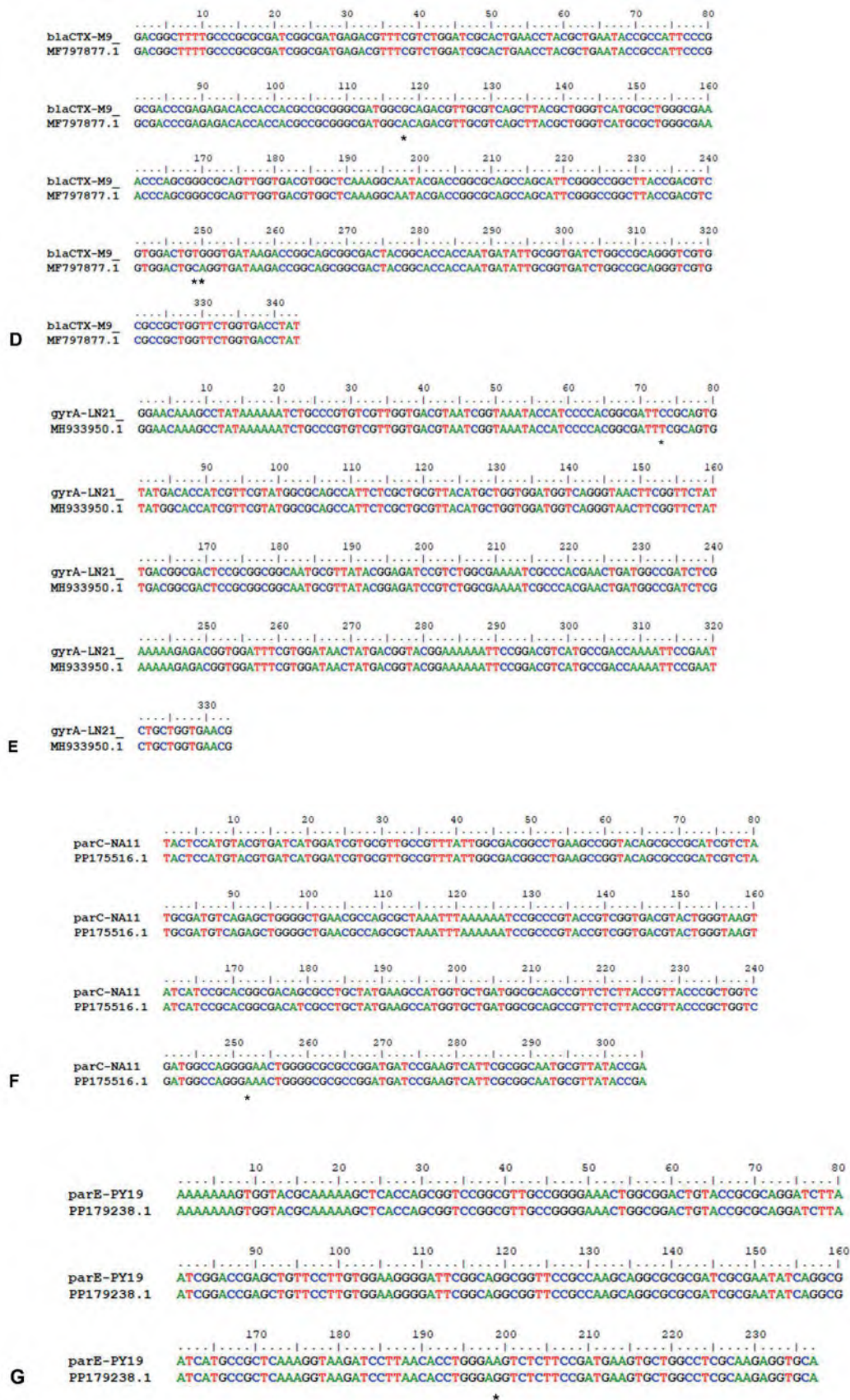
Figure 2. Heatmap displaying the distribution pattern in *Salmonella* serogroups. A: antimicrobial resistance determinants, B: resistance. The determinants and 12 antimicrobial patterns are categorized following extended-spectrum β -lactamases (ESBLs), quinolone-resistance-determining regions (QRDR), and plasmid-mediated quinolone resistance (PMQR), identified in ESBL producer and quinolone strains (N=38). The color gradient, from blue (0) to red (15), indicates the number of isolates per serogroup for each resistance determinant and pattern.

Table 3. Antimicrobial resistance profiles and genotypic of ESBL producer and Quinolone resistance in *Salmonella* isolates from pork sold in retail markets in Northern Thailand.

Serogroup	Pattern of resistance (n)	Quinolone and ESBL gene (N)
A (N=2)	NA (2)	<i>gyrA/parC</i> (1) <i>gyrA</i> (1)
B (N=7)	TE/NA (1) AMP/NA (1) AMP/TE/NA (2) AMP/C/NA/S/GEN (1) AMP/TE/C/CTX/CAZ/CPM/CTR (1) AMP/TE/CPZ/C/NA/S/AMC/CTX/CAZ/ CZX/CTR (1)	<i>gyrA/parC</i> (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC</i> (2) <i>gyrA/parC/parE/qnrA</i> (1) <i>bla</i> _{CTX-M-2} / <i>bla</i> _{CTX-M-9} (1) <i>gyrA/parC/parE</i> (1)
C (N=15)	NA (4) NA/S (1) TE/NA/S (2) AMP/TE/CPZ/NA/IPM (1) AMP/TE/CPZ/COT/NA/S (1) AMP/TE/CPZ/C/COT/NA/S/AMC (1) AMP/TE/CPZ/C/NA/S/AMC/IPM/GAT/ NX/OF (1) AMP/TE/CPZ/NA/AMC/IPM/GAT/NX/ OF/LE/CIP (1) AMP/TE/CPZ/C/NA/S/CTX/GEN/CAZ/ CZX/CPM/ CTR/AT (1) AMP/CPZ/NA (1) NA/CTX/CZX/AMC (1)	<i>gyrA/parC</i> (1) <i>gyrA/parC/parE</i> (2) <i>gyrA/parC/parE/qnrS</i> (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC/parE/qnrA/qnrS</i> (2) <i>gyrA/parC/parE/qnrS</i> (1) <i>gyrA/parC/parE/qnrS</i> (1) <i>gyrA/parC/parE/qnrS/aac(6')-Ib-cr</i> (1) <i>gyrA/parC/parE/qnrS</i> (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC/parE/qnrS/bla</i> _{TEM} / <i>bla</i> _{CTX-M-1} (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC/qnrB</i> (1)
D (N=1)	AMP/TE/C/NA/S/IPM/GAT/NX/OF/LE (1)	<i>gyrA/parC/parE</i> (1)
E (N=11)	NA (3) TE/C/NA (1) AMP/NA/COT/C (1) AMP/TE/NA/S (1) AMP/TE/C/COT/NA (2) AMP/TE/CPZ/C/COT/NA/CTX/GEN/CAZ/CZX/CPM/ CTR/IPM/AT/CIP (1) AMP/COT/NA/S (1) AMP/CPZ/COT/NA/S (1)	<i>gyrA/parC</i> (2) <i>parC/parE</i> (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC/parE</i> (1) <i>gyrA/parC</i> (1) <i>gyrA/parC/parE/qnrS</i> (1) <i>parC/parE/qnrD/qnrS</i> (1) <i>gyrA/parC/parE/qnrS/bla</i> _{TEM} / <i>bla</i> _{CTX-M-1} (1) <i>gyrA/parC/parE/qnrS</i> (1) <i>gyrA/parC/parE/qnrS</i> (1)
G (N=1)	AMP/TE/C/COT/NA (1)	<i>gyrA/parC/parE/qnrA</i> (1)
I (N=1)	NA (1)	<i>gyrA/parC/parE/qnrS</i> (1)

Note: AMP: ampicillin, AMC: amoxicillin-clavulanate acid, AT: Aztreonam, CPM: cefepime, CPZ: cefoperazone, CTX: cefotaxime, FOX: ceftazidime, CTR: ceftazidime, CZX: ceftazidime, C: chloramphenicol, CIP: ciprofloxacin, GAT: gatifloxacin, GEN: gentamicin, IPM: imipenem, LE: levofloxacin, NA: nalidixic acid, NX: norfloxacin, OF: ofloxacin, S: streptomycin, TE: tetracycline, COT or SXT: trimethoprim/sulfamethoxazole.





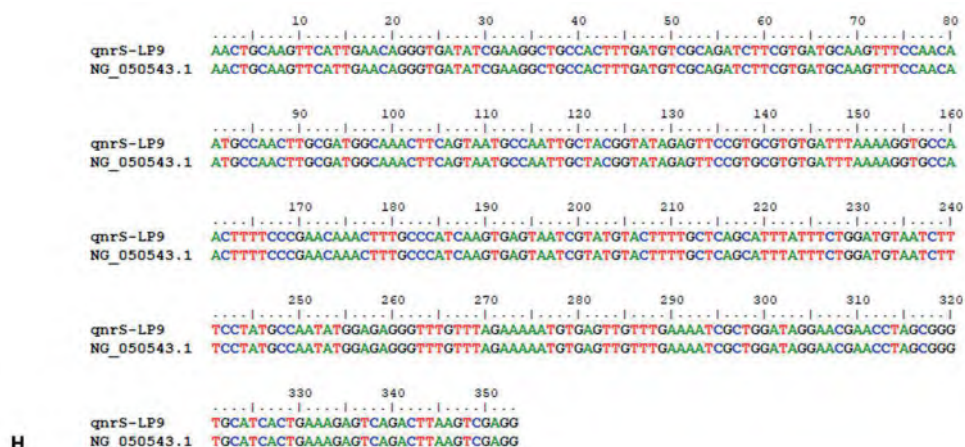


Figure 3. Sequences alignment of 4 types of ESBL genes. A: *bla*_{TEM}, B: *bla*_{CTX-M-1}, C: *bla*_{CTX-M-2}, D: *bla*_{CTX-M-9} and 4 quinolone resistance determinants, E: *gyrA*, F: *parC*, G: *parE*, H: *qnrS*) against sequences available in the GenBank nucleotide database as a reference. The position of the nucleotide mutation is indicated with *.

Discussion

The present study showed a high prevalence of *Salmonella* isolated from pork samples collected in retail pork shops from 7 different provinces in Northern Thailand. The prevalence of *Salmonella* isolated in this study (98.8%) was notably higher than that reported in studies conducted in Bangkok, Thailand (27.6%), and other countries: Cambodia (45.1%), Vietnam (69.7%), China (73.1%) and United states (outbreak) (10.0%).¹⁹⁻²³ This high prevalence might be attributable to regional differences in pork production practices or variation in sample collection and isolation methods. Nine distinct serogroups were identified, with serogroup C (50.9%) being the most common. This finding is consistent with a previous study conducted in Phayao, Thailand, where 54.8% of isolates belonged to serogroup C.¹⁴ Although serogroup C can be further subdivided into C1 and C2, our study did not differentiate between these subgroups, which could have provided more detailed epidemiological insights. Serogroup C is known to be responsible for a significant proportion of *Salmonella* infections in humans and animals.²⁴ The distribution of serovar worldwide varies widely from continent to continent.²⁵

In this study, 23 antimicrobials were tested, and most *Salmonella* isolates were resistant to AMP (55.6%). This study's most prevalent resistance pattern was AMP/TE/SXT (4.7%), lower than the 19.1% reported in a previous study from the same region.¹⁴ These antibiotics are commonly used in clinical settings, potentially leading to the development of resistance. The resistance rates to cephalosporins observed in this study (about 5.0%) were higher than those reported in other studies from Thailand.^{4,26} Our findings revealed that nearly half (49.0%) of the isolates were multidrug-resistant (MDR), consistent with previous research conducted in Thailand.^{13,19} However, the prevalence was lower than that observed in studies from China.²³ The low rate of ESBL-producing *Salmonella* (1.8%) detected aligns with other reports from Thailand,

although it is lower than rates observed in prior studies from the same area.⁴ The presence of isolates resistant to third- and fourth-generation cephalosporins is particularly concerning, as these drugs are crucial for treating severe bacterial infections.

Resistance to nalidixic acid (NA) was the most frequently detected in this study, though the prevalence was lower compared to studies conducted in China and other parts of Thailand.^{13,18} NA was approved by the United States Food and Drug Administration (FDA) in 1964 as a first-generation quinolone that is no longer used in humans or animals. However, its resistance is significant because it may indicate emerging resistance to fluoroquinolones globally used to treat respiratory diseases in swine.^{27,28} The persistence of NA resistance suggests that *Salmonella* isolates may have retained this resistance as an onset to broader fluoroquinolone resistance.²⁹ Given the continued use of antibiotics such as penicillin, tetracycline, and fluoroquinolones in swine infection in Thailand, the emergence of MDR *Salmonella* is a pressing public health concern.³⁰ The low usage of cephalosporins in this region might explain the limited distribution of ESBL producers; however, co-selection of ESBL genes by other commonly used antibiotics remains a possibility.⁴ This study observed susceptibility to ertapenem and meropenem, which was consistent with a survey that reported a low rate of meropenem resistance (0.46%) in salmonellosis patients in Central Thailand from 2011 to 2020.³¹

Among the detected ESBL genes in this study, the *bla*_{TEM} and *bla*_{CTX-M-1} genes were the most identified. This finding aligns with previous reports from Thailand, where *bla*_{CTX-M-1} and *bla*_{TEM} are frequently detected in ESBL-producing *Salmonella*.^{4,26} In our finding, *parC* was the most common quinolone-mediated resistance determinant detected, followed by *gyrA* and *parE*. Furthermore, it was interesting that co-existed of quinolone resistance determinants and β -lactam resistance genes (*gyrA/parC/parE/qnrS/bla*_{TEM}/*bla*_{CTX-M-1} and *gyrA/parC/parE/qnrS/*

*bla*_{TEM}/*bla*_{CTX-M-1}) were observed in 2 *Salmonella* isolates. This indicates that a quinolone-mediated resistance determinant may be closely related to the β -lactam resistance genes in *Salmonella*. Similar to previous studies, quinolone-mediated resistance determinants in ESBL-producing *Salmonella* strains were detected.^{32,33}

Additionally, the mutation within *gyrA* was present in all NA-resistant isolates, consistent with its role in driving resistance to quinolones in *Salmonella*. Fluoroquinolone resistance is typically associated with mutations in the quinolone resistance-determining regions (QRDR) and the presence of plasmid-mediated quinolone resistance (PMQR) regions.²⁹ In the present study, *gyrA*/*parC*/*parE* was the most frequent pattern, which agrees with a previous study reported in 2018.³⁴ In general, the mutations at codon 83, 87, and 133 in *gyrA* and a mutation at M438I in the *parE* are associated with the resistance to quinolones with high prevalence.^{35,36} In addition, previous studies indicated that point mutations in *parC* and *parE* were also observed with the concomitant presence of mutation within *gyrA*.³⁷ This mutation contributes to quinolone resistance, particularly to nalidixic acid (NA), which agrees with this study's high incidence of resistance to NA. However, the point mutations of QRDR in all *Salmonella* isolates were not analyzed, which is one of the limitations of this study.

The predominant plasmid-mediated quinolone resistance (PMQR) regions identified include *qnrA*, *qnrB*, *qnrS*, and *aac(6')-Ib-cr*. The present investigation indicates that PMQR genes are less prevalent than QRDR genes. The *qnrS* was detected at 8.8% in the current study, which is lower when compared to research that indicated *qnrS* to be the most common gene among *Salmonella* strains recovered from different sources and regions such as retail meats and beef carcasses in Egypt (35.5%) and chicken in China (19.25%).^{32,38} The differences in host origin, geography, and the implementation of antibiotic policies all had an impact on the fluctuation of detection rates of these resistant genes. Further investigation into the specific mutations associated with fluoroquinolone resistance in *Salmonella* isolates from pork is warranted to understand the full scope of resistance mechanisms in this region.

In the present study, *Salmonella* strains were classified into serogroups, which are our limitations. Moreover, this research has focused on the specific area only in Northern Thailand. Thus, classification of *Salmonella* using serotype and wider geographical location needs to be done for further study. For ESBL gene detection among all ESBL producers, our study did not detect other resistance genes that might confer resistance to β -lactams. It was interesting to perform different ESBL genes such as *bla*_{PER}, *bla*_{OXA} and *bla*_{VEB} or other specific groups of *bla*_{CTX-M} and *bla*_{TEM}. In Thailand, there is very limited data on AMR in pork. Cross-contamination between foodstuffs at the retail markets should be considered due to the presence of *Salmonella* in the food contact surface, which is difficult to eradicate in the retail environment and facilities.³⁹ Our study has shown the prevalence and the recent pattern

of AMR of *Salmonella* isolates in the Northern part of Thailand, suggesting the potential drugs for antimicrobial therapy. The ESBL genes and fluoroquinolone resistance determinants in *Salmonella* pork isolates must be further identified nationwide to propose local or national policy on antibiotic usage and food safety.

Conclusion

In conclusion, this study provides critical insights into *Salmonella*'s prevalence and antimicrobial resistance (AMR) patterns in pork from Northern Thailand. The distribution of MDR and the correlation between the phenotypic and the genotypic susceptibilities found were described, showcasing the great concern about the spread of resistant *Salmonella* strains in Northern Thailand. The findings underscore the need for ongoing surveillance and the implementation of stringent antimicrobial stewardship practices in pork production. Cross-contamination between foodstuffs at retail markets should be closely monitored, as *Salmonella* contamination on food contact surfaces poses a significant challenge to food safety and public health. To mitigate the risks, continuous monitoring of antibiotic susceptibility is necessary.

Moreover, education about reasonable antimicrobial use in swine farms should be promoted. For the butchers, education about good hygiene should be established to reduce the transmission and emergence of MDR *Salmonella* as zoonotic foodborne pathogenic bacteria. For further study, we will monitor the prevalence of *Salmonella* risk at the beginning of the pork production stage and assess the genetic characterization of mutations associated with fluoroquinolone resistance and ESBL genes.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Dewey-Mattia D MK, Hall AJ, Wise ME, Crowe SJ. Surveillance for Foodborne Disease Outbreaks — United States, 2009-2015. MMWR Surveill Summ. 2018; 67(10): 1-11. doi: 10.15585/mmwr.ss6710a1
- [2] Aslam B, Khurshid M, Arshad MI, Muzammil S, Rasool M, Yasmeeen N, et al. Antibiotic resistance: One health one world outlook. Front Cell Infect Microbiol. 2021; 11: 771510. doi: 10.3389/fcimb.2021.771510.
- [3] Hosain MZ, Kabir SML, Kamal MM. Antimicrobial uses for livestock production in developing countries. Vet World. 2021; 14(1): 210-21. doi: 10.14202/vetworld.2021.210-221.
- [4] Lay KK, Jeamsripong S, Sunn KP, Angkititrakul S,

- Prathan R, Srisanga S, et al. Colistin resistance and ESBL production in *Salmonella* and *Escherichia coli* from pigs and pork in Thailand, Cambodia, Lao PDR, and Myanmar border area Antibiotics (Basel). 2021; 10(6): 657. doi: 10.3390/antibiotics10060657.
- [5] Pungpian C, Lee S, Trongjit S, Sinwat N, Angkititrakul S, Prathan R, et al. Colistin resistance and plasmid-mediated *mcr* genes in *Escherichia coli* and *Salmonella* isolated from pigs, pig carcass and pork in Thailand, Lao PDR and Cambodia border provinces. J Vet Sci. 2021; 22(5): e68. doi: 10.4142/jvs.2021.22.e68.
- [6] Meunsene D, Eiamsam-Ang T, Patchanee P, Pascoe B, Tadee P, Tadee P. Molecular evidence for cross boundary spread of *Salmonella* spp. in meat sold at retail markets in the middle Mekong basin area. PeerJ. 2021; 9: e11255. doi: 10.7717/peerj.11255.
- [7] Niyomdech N, Mungkornkaew N, Samosornsuk W. Serotypes and antimicrobial resistance of *Salmonella* Enterica isolated from pork, chicken meat and lettuce, Bangkok and Central Thailand. Southeast Asian J Trop Med Public Health. 2016; 47(1): 31-9.
- [8] Prasertsee T, Chokesajjawatee N, Santiyanont P, Chuammitri P, Deudom M, Tadee P, et al. Quantification and rep-PCR characterization of *Salmonella* spp. in retail meats and hospital patients in Northern Thailand. Zoonoses Public Health. 2019; 66(3): 301-9. doi: 10.1111/zph.12565.
- [9] Bergspica I, Kaprou G, Alexa EA, Prieto M, Alvarez-Ordóñez A. Extended spectrum beta-lactamase (ESBL) producing *Escherichia coli* in pigs and pork meat in the European Union. Antibiotics (Basel). 2020; 9(10): 678. doi: 10.3390/antibiotics9100678.
- [10] Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. Lancet Infect Dis. 2006; 6(10): 629-40. doi: 10.1016/S1473-3099(06)70599-0.
- [11] Wiener ES, Heil EL, Hynicka LM, Johnson JK. Are fluoroquinolones appropriate for the treatment of extended spectrum beta-lactamase-producing gram-negative bacilli? J Pharm Technol. 2016; 32(1): 16-21. doi: 10.1177/8755122515599407.
- [12] World health organization. Critically important antimicrobials for human medicine: WHO: Geneva, Switzerland; 2012 Available from: http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf?ua=1&ua=1.
- [13] Phongaran D, Khang-Air S, Angkititrakul S. Molecular epidemiology and antimicrobial resistance of *Salmonella* isolates from broilers and pigs in Thailand. Vet World. 2019; 12(8): 1311-8. doi: 10.14202/vetworld.2019.1311-1318.
- [14] Nuanmuang N, Kummasook A. Prevalence and antimicrobial resistance of *Salmonella* in minced pork from retail shops around the University of Phayao, Thailand. Asian Health, Science and Technology Reports (AHSTR). 2018; 26(4): 9-16. doi: 10.14456/nujst.2018.17.
- [15] International organization for standardization. ISO 6579-1:1993. Microbiology of food and animal feeding stuffs Horizontal method for the detection of *Salmonella* spp. Part 1: General guidelines. Geneva: ISO; 1993.
- [16] World Health Organization collaborating centre for reference and research on *Salmonella*. Antigenic formulae of the *Salmonella* serovars. 2007. Available from: https://www.pasteur.fr/sites/default/files/veng_0.pdf.
- [17] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(3): 268-81. doi: 10.1111/j.1469-0691.2011.03570.x.
- [18] Wang J, Li Y, Xu X, Liang B, Wu F, Yang X, et al. Antimicrobial resistance of *Salmonella* enterica Serovar Typhimurium in Shanghai, China. Front Microbiol. 2017; 8: 510. doi: 10.3389/fmicb.2017.00510.
- [19] Kong-Ngoen T, Santajit S, Tunyong W, Pumirat P, Sookrung N, Chaicumpa W, et al. Antimicrobial resistance and virulence of non-Typhoidal *Salmonella* from retail foods marketed in Bangkok, Thailand. Foods. 2022; 11(5): 661. doi: 10.3390/foods11050661.
- [20] Rortana C, Nguyen-Viet H, Tum S, Unger F, Boqvist S, Dang-Xuan S, et al. Prevalence of *Salmonella* spp. and *Staphylococcus aureus* in chicken meat and pork from Cambodian markets. Pathogens. 2021; 10(5): 556. doi: 10.3390/pathogens10050556.
- [21] Nguyen DT, Kanki M, Nguyen PD, Le HT, Ngo PT, Tran DN, et al. Prevalence, antibiotic resistance, and extended-spectrum and AmpC beta-lactamase productivity of *Salmonella* isolates from raw meat and seafood samples in Ho Chi Minh City, Vietnam. Int J Food Microbiol. 2016; 236: 115-22. doi: 10.1016/j.ijfoodmicro.2016.07.017.
- [22] Dewey-Mattia D, Manikonda K, Hall AJ, Wise ME, Crowe SJ. Surveillance for foodborne disease outbreaks - United States, 2009-2015. MMWR Surveill Summ. 2018; 67(10): 1-11. doi: 10.15585/mmwr.ss6710a1.
- [23] Zhang L, Fu Y, Xiong Z, Ma Y, Wei Y, Qu X, et al. Highly prevalent multidrug-resistant *Salmonella* from chicken and pork meat at retail markets in Guangdong, China. Front Microbiol. 2018; 9: 2104. doi: 10.3389/fmicb.2018.02104.
- [24] Brenner FW, Villar RG, Angulo FJ, Tauxe R, Swaminathan B. *Salmonella* nomenclature. J Clin Microbiol. 2000; 38(7): 2465-7. doi: 10.1128/JCM.38.7.2465-2467.2000.
- [25] Fuche FJ, Sow O, Simon R, Tennant SM. *Salmonella* Serogroup C: Current status of vaccines and why they are needed. Clin Vaccine Immunol. 2016; 23(9): 737-45. doi: 10.1128/cvi.00243-16.
- [26] Trongjit S, Angkititrakul S, Tuttle RE, Pongserree J, Padungtod P, Chuanchuen R. Prevalence and antimicrobial resistance in *Salmonella* enterica isolated from broiler chickens, pigs and meat products in Thailand-Cambodia border provinces. Microbiol Immunol. 2017; 61(1): 23-33. doi: 10.1111/1348-04

21.12462.

- [27] Pham TDM, Ziora ZM, Blaskovich MAT. Quinolone antibiotics. *Medchemcomm*. 2019; 10(10): 1719-39. doi: 10.1039/c9md00120d.
- [28] Mercer MA. Quinolones, Including Fluoroquinolones, Use in Animals MSD Veterinary Manual: MSD Veterinary Manual; 2022. Available from: <https://www.msdsvet-manual.com/pharmacology/antibacterial-agents/quinolones-including-fluoroquinolones-use-in-animals>.
- [29] Yin X, Dudley EG, Pinto CN, M'Ikanatha N M. Fluoroquinolone sales in food animals and quinolone resistance in non-typhoidal *Salmonella* from retail meats: United States, 2009-2018. *J Glob Antimicrob Resist*. 2022; 29: 163-7. doi: 10.1016/j.jgar.2022.03.005.
- [30] Cameron-Veas K, Fraile L, Napp S, Garrido V, Grillo MJ, Migura-Garcia L. Multidrug resistant *Salmonella* enterica isolated from conventional pig farms using antimicrobial agents in preventative medicine programmes. *Vet J*. 2018; 234: 36-42. doi: 10.1016/j.tvjl.2018.02.002.
- [31] Hengkrawit K, Tangjade C. Prevalence and trends in antimicrobial susceptibility patterns of multi-drug-resistance non-Typhoidal *Salmonella* in Central Thailand, 2012-2019. *Infect Drug Resist*. 2022; 15: 1305-15. doi: 10.2147/IDR.S355213.
- [32] Chen Y, Liu L, Guo Y, Chu J, Wang B, Sui Y, et al. Distribution and genetic characterization of fluoroquinolone resistance gene *qnr* among *Salmonella* strains from chicken in China. *Microbiol Spectr*. 2024; 12(4): e0300023. doi: 10.1128/spectrum.03000-23.
- [33] Nwosu UO, Ibiam FA, Amadi-Ibiam CO, Iroha CS, Edemekong CI, Peter IU, et al. Fecal carriage of extended spectrum beta-lactamase and fluoroquinolone resistant gene in non-typhoidal *Salmonella* enterica isolates from food-producing animals and humans. *Journal of Drug Delivery and Therapeutics*. 2023; 13(9): 128-34. doi: 10.22270/jddt.v13i9.5964.
- [34] Kuang D, Zhang J, Xu X, Shi W, Chen S, Yang X, et al. Emerging high-level ciprofloxacin resistance and molecular basis of resistance in *Salmonella* enterica from humans, food and animals. *Int J Food Microbiol*. 2018; 280: 1-9. doi: 10.1016/j.ijfoodmicro.2018.05.001.
- [35] Qian H, Cheng S, Liu G, Tan Z, Dong C, Bao J, et al. Discovery of seven novel mutations of *gyrB*, *parC* and *parE* in *Salmonella* Typhi and Paratyphi strains from Jiangsu Province of China. *Sci Rep*. 2020; 10(1): 7359. doi: 10.1038/s41598-020-64346-0.
- [36] Ngoi ST, Thong KL. High resolution melting analysis for rapid mutation screening in gyrase and Topoisomerase IV genes in quinolone-resistant *Salmonella* enterica. *Biomed Res Int*. 2014; 2014: 718084. doi: 10.1155/2014/718084.
- [37] Gu Y, Huang L, Wu C, Huang J, Hao H, Yuan Z, et al. The evolution of fluoroquinolone resistance in *Salmonella* under exposure to sub-inhibitory concentration of enrofloxacin. *Int J Mol Sci*. 2021; 22(22): 12218. doi: 10.3390/ijms222212218.
- [38] Adel WA, Ahmed AM, Hegazy Y, Torky HA, Shimamoto T. High prevalence of ESBL and plasmid-mediated quinolone resistance genes in *Salmonella* enterica isolated from retail meats and slaughterhouses in Egypt. *Antibiotics (Basel)*. 2021; 10(7): 881. doi: 10.3390/antibiotics10070881.
- [39] Eiamsam-ang T, Tadee P, Pascoe B, Patchanee P. Genome-based analysis of infrequent *Salmonella* serotypes through the Thai pork production chain. *Frontiers in Microbiology*. 2022; 13: 968695. doi: 10.3389/fmicb.2022.968695.

Thumb carpometacarpal joint immobilization orthosis

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ABSTRACT

Background: A new design of thumb carpometacarpal joint immobilization orthosis for positioning and improving hand function. This orthosis stabilizes the thumb in the desired position when thenar muscles are weakened, first carpometacarpal joint pain, deformities, or other thumb problems. This orthosis frees the dorsum of the hand, covers the palm, curves and conforms to the thenar web space, and holds the thumb in opposition.

Objective: To study compliance and acceptance of patients with the new design thumb carpometacarpal joint immobilization orthosis that is easy to fabricate and reduces cost.

Materials and methods: This pilot study was set at the Occupational Therapy Unit, Department of Rehabilitation Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. All twelve patients, including seven of first carpometacarpal joint arthritis, two Syringomyelia, two median nerve injuries, and one cerebral palsy, were asked to fill out a questionnaire designed for hand function and activities of daily living. In contrast, the thumb carpometacarpal joint immobilization orthosis was fabricated. After the patient had worn the new design orthosis for two weeks, they were asked to complete two questionnaires. One was hand function and activities of daily living, and the other was five items of patients' satisfaction with thumb carpometacarpal joint immobilization orthosis that was found out from the factors related to compliance with hand orthosis.

Results: After two weeks, all patients who applied a thumb carpometacarpal joint immobilization orthosis could improve the quality of writing, open doors, and pick up small coins. They all accepted thumb carpometacarpal joint immobilization orthosis to take turns applying with thumb spica because free space at the dorsum of the hand permitted them to move more flexibly with excellent support at the first carpometacarpal joint, letting them tolerate long-term activities.

Conclusion: The new thumb carpometacarpal joint immobilization orthosis focuses on thumb opposition and allows free movement of the wrist and metacarpophalangeal joints, especially in the case of carpometacarpal joint arthritis who do not have a weak thumb. It can be substituted for another thumb opposition orthosis because of easy fabrication and reduced cost.

Introduction

The thumb is the most critical finger for performing hand functions and is involved in activities of daily living. Therefore, the opposition of the thumb is a complex and vital movement.^{1,2} When we performed this position, the thumb pad should touch the pad of the other fingers.² The carpometacarpal and metacarpophalangeal joints of the thumb should move palmar abduction to expand the first web space for adequate opposition. This position worked with thenar muscles (abductor pollicis brevis, flexor pollicis brevis, and opponens pollicis).²

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The functional position of the thumb means that the thumb keeps palmar abduction of 45°, opposition, and maintains first web space for prehension in both active and passive movement.² Both permanent and temporary thumb carpometacarpal joint immobilization orthosis referenced the principle of orthosis to consider patients' anatomy, biomechanics, and compliance.³⁻⁵ For median nerve injury, spinal cord injury (C6, 7 levels), cerebral palsy, and syringomyelia, patients with the weak thumbs (Figure 1)

needed a thumb carpometacarpal joint immobilization orthosis with thumb support to promote more thumb stability. A group of carpometacarpal joint arthritis patients who could do thumb movement (Figure 2) have received a thumb carpometacarpal joint immobilization orthosis without thumb support for correcting joint deformities such as subluxation, hyperextension, deviation, and adduction contracture.



Figure 1. Ape hand deformity.



Figure 2. Thumb deformity.

A common orthosis for most thumb problems was thumb spica⁶ (butterfly pattern), which was very effective. Still, this orthosis took a long time to fabricate and needed a large area of thermoplastic (5"x 5"). Creating those orthoses can be challenging for therapists, especially for those who lack practical experience due to the complicated designs, patterns, and orthoses' requirements, which need to cover patients' volar and dorsum of hand and thumb areas. Additionally, therapists are often constrained by a tight time frame, typically having only 2-3 minutes to complete the process before thermoplastic is set. Usually, making one functional thumb orthosis requires the assistants to help set the position, and sometimes, it is necessary to adjust it until it fits patients' hands perfectly.

The patient's complaints regarding wearing butterfly pattern orthosis were the limited space in the thumb area, which makes it challenging to wear, especially in patients with wounds, sensitive skin, joint deformities, or muscle/ligament contracture. While wearing the thumb orthoses, patients might find them uncomfortable or painful at the dorsum of the hand when they do activities for a long time. The other is that the cost of orthosis is relatively high because it requires a large area of thermoplastic.

Therapists' problems while making butterfly pattern orthoses were difficulty setting the orthosis into the needed

positions and excessive use of thermoplastic because many areas need to be cut off in the making process. For all these reasons, the researchers aim to invent a new design of "Thumb carpometacarpal joint immobilization orthosis" and study its effectiveness, patient satisfaction, and compliance.

Orthoses designs

Two patterns were used for this thumb orthosis design, shown in Figures 3 and 4. Therapists must consider providing patients with the appropriate and correct type of orthosis based on the following criteria.

The thumb orthosis pattern in Figure 3 is designed for patients who can perform thumb opposition movements, such as carpometacarpal joint arthritis, subluxation, deviation, and adduction contracture patients. This orthosis pattern strongly supports the first carpometacarpal joint. The therapist started fabricating a thumb carpometacarpal joint immobilization orthosis by preparing a 3"x 5" thermoplastic with 3.2-mm thickness, cut in a rectangle shape. Figure 5 shows the steps of making a carpometacarpal joint immobilization orthosis pattern.

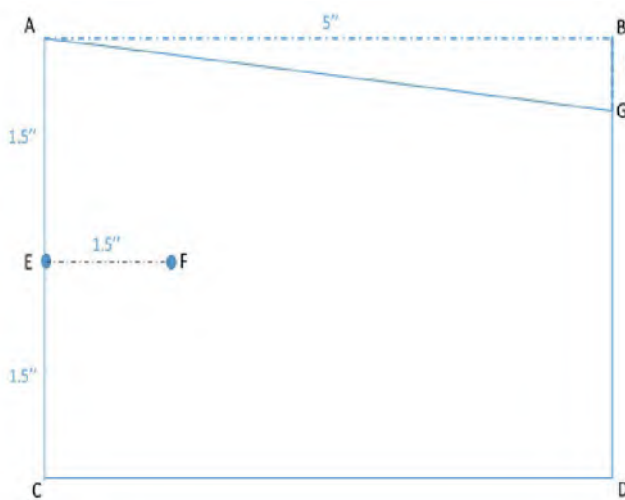


Figure 3. Thumb carpometacarpal joint immobilization orthosis pattern.

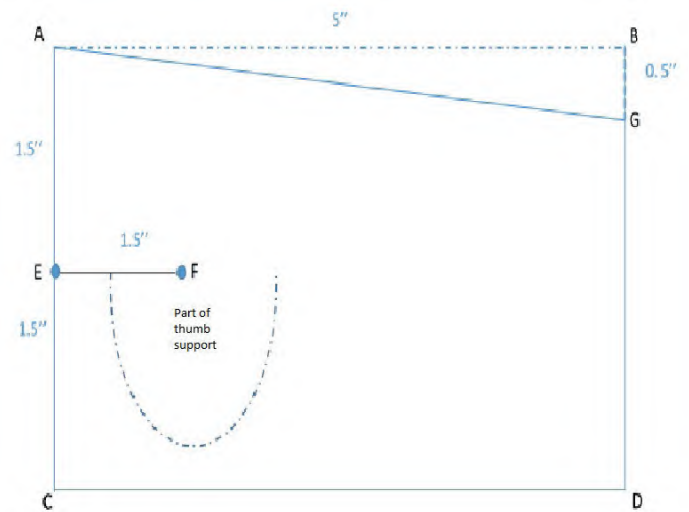


Figure 4. Thumb carpometacarpal joint immobilization orthosis with thumb support pattern.

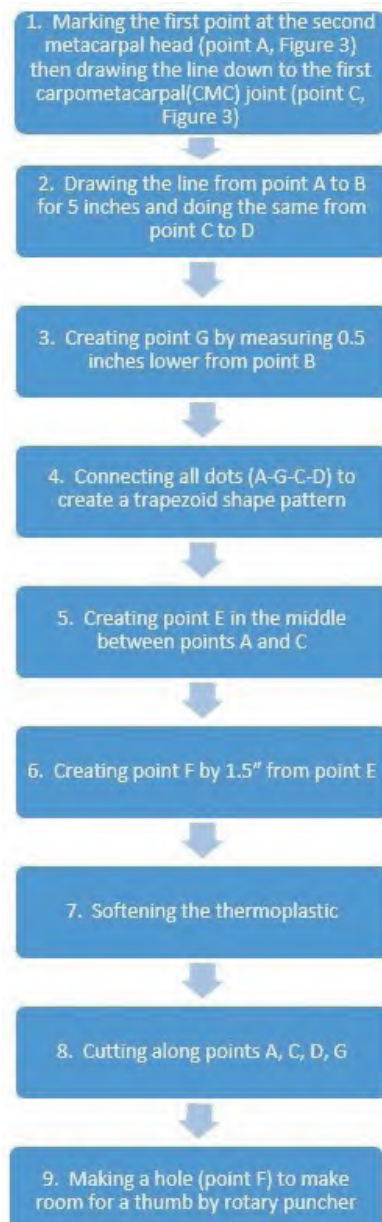


Figure 5. Steps of making a pattern of thumb carpometacarpal joint immobilization orthosis.

Materials and methods

Materials

1. Thermoplastic 3.2 mm. thickness (3"x 5")
2. Velcro 2" width loop
3. Velcro 2" width adhesive hook
4. Rotator puncher
5. Scissors
6. Heat gun

Methods

The therapist should start by marking the first point at the second metacarpal head (point A, Figure 3) and then drawing the line down to the first carpometacarpal (CMC) joint (point C, Figure 3). After that, draw the line from point A to B for 5 inches and do the same from point C to D. Next, create point G by measuring 0.5 inches lower from point B and connecting all dots (A-G) to create a

trapezoid shape pattern. Then, create point E in the middle between points A and C. Create point F by 1.5" from point E to get the perfect pattern of thumb carpometacarpal joint immobilization orthosis that could follow 1-9 steps (Figure 5). Softening the thermoplastic and cutting along points A, C, D, and G. The last process is punching point F to make room for a thumb by a rotary puncher.

The pattern of thumb orthosis was softened again, with the patient's thumb in a designated hole and gently molding thermoplastic to set the thumb in an opposing position. While setting the position, therapists must ensure that the transverse arch of the hand maintains a normal angle. The medial side of this orthosis should extend to cover the medial border of the head and base of the 2nd metacarpal bone. In contrast, the ulnar side should encompass the ulnar border of the 5th metacarpal bone (Figure 6).



Figure 6. The new design thumb carpometacarpal joint immobilization orthosis.

Figure 4 demonstrates the pattern of thumb orthosis for patients who could not perform thumb opposition movement because of weakness or pain. This pattern was created to provide more support to set the thumb into the needed position than the Figure 3 pattern. For example, median nerve injury, spinal cord injury, stroke, degenerative joint disease, and syringomyelia patients. We started by drawing a pattern from 1-9 steps (Figure 5) and drawing half oval as thumb's circumference size (base of thenar crease and radial side of the first metacarpal bone). Then pierced half of the oval circumference from the first metacarpophalangeal joint side. The therapist could set the position in thumb opposition, and the oval

piece will help to correct and support the thumb in the needed position (free IP or pad of thumb) (Figure 7). Due to the less area of thermoplastic for thumb orthosis (3"x 5") compared with thumb spica (5"x 5"), the cost of palmar thumb opposition orthosis is optimizing cost-effectiveness, it is around 40% lower than conventional butterfly pattern orthosis.

Wearing this orthosis is suggested both day and night.^{7,8} During the daytime, patients must remove the orthosis every two hours. When removing the orthosis, patients should perform gentle stretching and exercises for half an hour to rest and prevent skin breakdown.



Figure 7. The new design thumb carpometacarpal joint immobilization orthosis with thumb support.

Participants

Patients who had thumb problems and needed thumb orthoses, both old and new patients, were purposefully recruited based on the following criteria. Inclusion criteria are based on the weakness of thumb muscles, ape hand deformity from various causes such as median nerve, muscle imbalance or carpometacarpal joint arthritis. All of them were willing to sign the agreement to be involved in this study. Exclusion criteria were the patients with mental illness, stiffness or deformity at the wrist or other joints of the hands, other muscle weakness except for thumb weakness, communication problems, and other thumb problems such as trigger thumb and rheumatoid arthritis.

Data collection

The therapist screens patients by gathering patient's data, providing the study details, and letting them sign the consent form. Then, interviews will be conducted with patients to collect their medical histories and a questionnaire on hand function and activities of daily living evaluation will be administered. Patients received the thumb orthosis within 20-30 minutes. Therapists let them wear it for two weeks. After two weeks, therapists will explore the patient's satisfaction and hand function results. Patients had to complete a questionnaire about hand function and activities of daily living evaluation and a questionnaire of about five items of satisfaction for thumb carpometacarpal joint immobilization orthosis.

Instruments

The research instruments in this study were a self-development questionnaire on hand function and activities of daily living evaluation (Appendix 1), and a questionnaire on patients' satisfaction with thumb carpometacarpal joint immobilization orthosis assessed all patients' problems while wearing orthosis and factors related to compliance with hand orthosis in our clinic. (Appendix 2)

Data analysis

Descriptive statistics presented the mean and standard deviation of the participant's demographic data and hand function questionnaire.

Venue of study

Occupational therapy outpatient unit, Department of Rehabilitation Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University by January-August 2019.

Results

Twelve patients were involved, resulting in the fabrication of sixteen thumb carpometacarpal joint immobilization orthoses. Eight males and four females were among these patients. The patient group comprised two individuals with Syringomyelia (both requiring both right and left orthoses), two patients with median nerve injuries, one with cerebral palsy, and seven suffering from carpometacarpal joint arthritis (two of them necessitating both right and left orthoses), as indicated in Table 1.

Table 1. Demographic characteristics of the patients (N=12).

Characteristic (N=12)	N (%)	
Age (year)	Range 7-76	Mean (SD) 40.08 (SD)
Gender		
Male		8 (66.67%)
Female		4 (33.33%)
Disability		
Ape hand		4 (33.34%)
Spastic hand (thumb)		1 (8.33%)
CMC joint subluxation		7 (58.33%)
Diagnosis		
Syringomyelia		2
Median nerve injury		2
Cerebral palsy		1
Arthritis		7
Number of carpometacarpal joint immobilization orthosis		
Left side		2
Right side		10
Both side		4

Thumb carpometacarpal joint immobilization orthosis could help the patients to do more fine hand functions such as picking up small objects, opening doors by using keys, and writing, especially when patients do those activities for a long time because of free space at the dorsum of the hand. It is essential to set the thumb position

as normal as possible while doing thumb opposition movement, which helps them do more instrumental daily activities, as shown in Figure 8. Only one cerebral palsy child did not have better hand function, but her hand position was better.

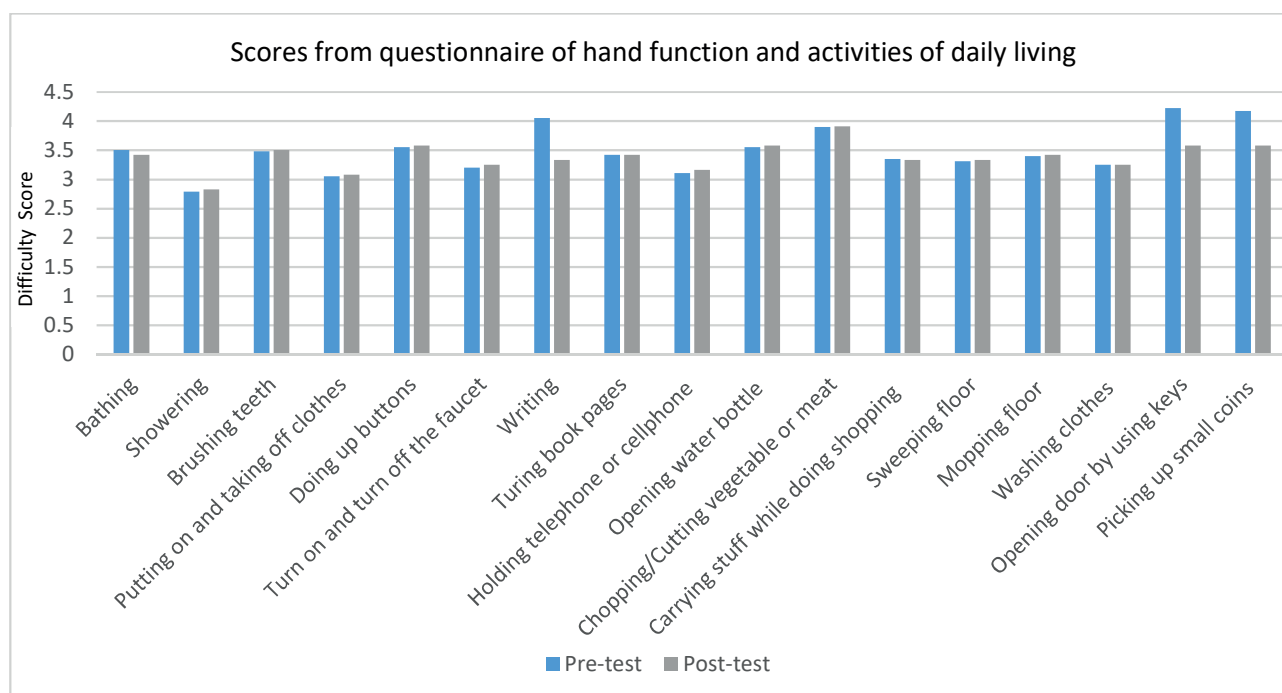


Figure 8. Comparison between pre-test and post-test questionnaires of hand function and activities of daily living (N=12).
 1: no difficulty, 2: a little bit of difficulty, 3: moderate difficulty, 4: quite a bit of difficulty,
 5: extreme difficulty or unable to perform activities

Carpometacarpal joint arthritis patients can apply thumb carpometacarpal joint immobilization orthosis without thumb support. They could move their thumb independently and feel free in the dorsum of their hands compared to previous thumb spica. For weak thumb patients, this thumb orthosis with thumb support and a free thumb pad, patients' thumb stability enabled them to do more movement.

There were seven carpometacarpal joint arthritis that applied thumb carpometacarpal joint immobilization orthosis without thumb support (Figure 6) correctly. Another patient applied thumb carpometacarpal joint immobilization orthosis with support (Figure 7). Notably, all seven carpometacarpal joint arthritis patients were

previously accustomed to a different pattern of thumb orthoses. However, after trying the thumb carpometacarpal joint immobilization orthosis, they unanimously preferred it for three primary reasons. Firstly, this orthosis provided exceptionally robust support. Secondly, it effectively established and corrected the thumb's carpometacarpal joint deformities. Lastly, it was easy for the patients to apply this orthosis independently. Notably, all patients reported that the aspect they liked the most about wearing the thumb carpometacarpal joint immobilization orthosis was experiencing less pain, particularly those who had previously used other types of thumb orthoses, as demonstrated in Table 2.

Table 2. Scores from a questionnaire of patients' satisfaction with thumb carpometacarpal joint immobilization orthosis (N=12).

No.	The number of answered items				
	Difficulty of wearing	Pain while wearing	Hand function while wearing	Follow doctor's advice	Valuable
1	6	8	8	9	8
2	8	9	8	10	8
3	7	9	9	10	7
4	2	9	7	8	10
5	10	10	7	10	10
6	10	10	7	8	10
7	10	10	10	10	10
8	10	8	8	5	8
9	6	10	9	9	7
10	9	10	8	10	9
11	8	9	8	9	9
12	6	8	8	8	8
MD	8	9	8	9	8.5
SD	7.67	9.16	8.08	8.83	8.67

Discussion

Orthosis is a standard conservative treatment for first carpometacarpal joint problems, providing pain relief, joint positioning, and hand function.⁹ This thumb carpometacarpal joint immobilization orthosis is an immobilization orthosis applied from many thumb orthosis patterns¹⁰⁻¹² for patients' comfort. Previous studies explained the effectiveness of palmar thumb opposition orthosis in various aspects.⁸

A therapist can use many patterns of thumb opposition orthosis^{1,10} to select the appropriate one for the patient. In our routine work, the therapist gave thumb spica (butterfly pattern) to thumb problem patients, and the effectiveness of this orthosis was agreed upon.³ However, for patients, the most critical concerns of orthosis were cost-effectiveness and comfort, so therapists tried thumb carpometacarpal joint immobilization orthosis to solve these problems. The pattern of thumb spica covered both the carpometacarpal joint and the metacarpophalangeal joint, even in unnecessary cases.

The results showed that a group of patients with carpometacarpal joint arthritis improved three activities of daily living (writing, opening doors by using keys, and picking up tiny coins). These three activities of daily living caused pain at the carpometacarpal joint. Strong support and sound position for more stability of carpometacarpal joint immobilization orthosis could solve pain problems and cause less difficulty while doing those activities.

Another group of patients consists of two Syringomyelia, two median nerve injuries, and one cerebral palsy. They were all severe and chronic cases. There was not much change as a result.

Conclusion

All the patients who had differently used different thumb orthoses expressed high satisfaction after

transitioning to the thumb carpometacarpal joint immobilization orthosis, particularly those suffering from first carpometacarpal osteoarthritis with pain and/or subluxation. Patients cited several reasons for their contentment. First and foremost, the orthosis offered excellent support for the first carpometacarpal (CMC) joint by the medial and lateral aspects, while the lateral aspect of the thumb spica was Velcro. Additionally, it provided ample space on the dorsum of the hand and resulted in less pressure.

From therapists' perspectives, these two orthoses' patterns proved time-efficient and had simpler designs than the older alternatives. Furthermore, these designs were cost-effective since they required less thermoplastic material for fabrication. The thumb carpometacarpal joint immobilization orthosis is proper for thumb problems. It is suitable for therapists to have a variety of thumb orthoses for patients.

Limitation

One limitation of this thumb carpometacarpal joint immobilization orthosis was the difficulty in facilitating certain functions that require a flat palm, such as holding large and heavy objects and pushing the door open.¹¹ This challenge arises from the intricate and complex movements of the thumb, which make it unique and crucial for hand function. Thence, therapists must consider the details of thumb anatomy and kinesiology.¹

Another limitation was that one question about pain in a satisfaction questionnaire about the thumb carpometacarpal joint immobilization orthosis might confuse patients. The score was converted to the pain score. Accordingly, therapists must describe pain clearly to patients before completing this questionnaire.

The last limitation was the lack of validity and reliability of both questionnaires about patients'

satisfaction with palmar thumb opposition orthosis and the questionnaire on hand function and activities of daily living evaluation in the Thai version.^{8,12} This thumb carpometacarpal joint immobilization orthosis was also studied in a small group of patients. Further research about palmar thumb opposition, questionnaires on hand function and activities of daily living, and a satisfaction questionnaire about the thumb carpometacarpal joint immobilization orthosis were necessary.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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None

Ethics consideration

This study was approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (Approval ID: COA NO. MURA2018/956)

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References

- [1] Veraldi TR. The Rectangle: A hand-based pattern for a dorsal short thumb opponens orthosis with metacarpophalangeal support. *J Hand Ther.* 2019; 32(3): 395-98. doi.org/10.1016/j.jht.2017.10.003.
- [2] Skirven TM., Osterman AL, Fedorczyk JM, *et al.* Rehabilitation of the hand: Surgery and therapy. 6th ed. St. Louis Missouri: Mosby-Year Book. Inc; 2011.
- [3] Fess EE. Splints: Mechanic versus convention. *J Hand Ther.* 1995; 8(2): 124-30. doi.org/10.1016/S0894-1130(12)80309-7.
- [4] Cannon N, Foltz R, Koepfor J, Lauk M, Simson D RB. *Manual of Hand Splinting.* New York: NY: Churchill Livingstone; 1985.
- [5] Gruschke JS HAR-MH, Van der Vegt AE, Van der Sluis CK. User perspectives on orthoses for thumb carpometacarpal osteoarthritis. *J Hand Ther.* 2019; 32(4): 435-43. doi.org/10.1016/j.jht.2018.04.006.
- [6] University of New Mexico School of Medicine [Internet]. USA: WebMSD; c2011-2024. How to apply a thumb spica splint; [updated Feb 2024; cited 2024 June 6]. Available from: <https://www.msdmanuals.com/professional/injuries-poisoning/how-to-splint-or-immobilize-an-upper-limb/how-to-apply-a-thumb-spica-splint>
- [7] Wang J., Erlandsson G., Rui YJ., Xu XH. Composite flexion splint for the stiff hand. *J Hand Ther.* 2011; 24: 66-8. doi.org/10.1016/j.jht.2010.09.068.
- [8] Arnold S., Janson R. Wrist extension or flexion mobilization orthosis: The dinosaur design. *J Hand Ther.* 2017; 30(1): 109-12. doi.org/10.1016/j.jht.2016.03.011.
- [9] Grenier ML. MR, Dalley P.,. The effectiveness of orthoses in the conservative management of thumb CMC joint osteoarthritis: An analysis of functional pinch strength. *J Hand Ther.* 2016; 29(3): 307-13. doi.org/10.1016/j.jht.2016.02.004.
- [10] Canteri-Tellez R. SD, Villafane JH., Arias JC. Short thumb opponens orthosis: A whale of a design. *J Hand Ther.* 2017; 30(1): 116-20. doi.org/10.1016/j.jht.2016.07.006.
- [11] Colditz JC. The biomechanics of a thumb carpometacarpal immobilization splint: design and fitting. *J Hand Ther.* 2000; 13(3): 228-35. doi.org/10.1016/S0894-1130(00)80006-X.
- [12] Algar L. NN, Ivy C., McGee C., Strouse S., Fedorczyk J. Assessment and treatment of nonsurgical thumb carpometacarpal joint osteoarthritis: A modified Delphi-based consensus paper of the American Society of Hand Therapists. *J Hand Ther.* 2023; 36(4): [982-99. doi.org/10.1016/j.jht.2023.08.008.

Appendix 1

แบบสอบถามเพื่อประเมินการใช้งานมือ

แบบสอบถามนี้ใช้เพื่อประเมินการใช้มือของท่านในการทำกิจกรรมประจำวันและทำงานบ้าน

โปรดตอบแบบสอบถามทุกข้อโดยทำเครื่องหมาย ✓ ในช่อง

กิจกรรม	ทำได้ตามปกติ (1)	ทำได้ด้วย ความลำบาก เล็กน้อย (2)	ทำได้ด้วย ความลำบาก ปานกลาง (3)	ทำได้ด้วย ความยาก ลำบากมาก (4)	ไม่สามารถ ทำได้ (5)
1. การอาบน้ำ					
- ใช้ขันตักอาบน้ำ					
- ใช้ฝักบัว					
2. การแปรงฟัน					
3. การถอด-ใส่เสื้อผ้า					
4. การกลัด-ถอดกระดุมเสื้อผ้า					
5. การเปิด-ปิดก๊อกน้ำหัวเกลียว					
6. การเขียนหนังสือ					
7. การพลิกหน้าหนังสือพิมพ์หรือพลิกหน้ากระดาษ					
8. การถือหูโทรศัพท์บ้านหรือถือโทรศัพท์มือถือเพื่อใช้งาน					
9. การเปิด-ปิดฝาเกลียวขวดหรือฝาเกลียวภาชนะ					
10. การหั่นผักหรือหั่นเนื้อสัตว์					
11. การถือหรือหิ้วของขณะช้อปปิ้งหรือขณะใช้งาน					
12. การทำงานบ้านได้แก่ - กวาดบ้าน - เช็ดบ้าน - ซักผ้า					
13. การจับกุญแจไขเปิดประตู					
14. การหยิบจับเหรียญบาท					

Appendix 2

แบบสอบถามความพึงพอใจของผู้ป่วยที่มีอาการอ่อนแรงของนิ้วหัวแม่มือและเกิด **ape hand deformity** ต่อการใช้อุปกรณ์พยุงนิ้วหัวแม่มือแบบ **palmar opposition splint**

โปรดกาเครื่องหมาย X ลงในช่องคะแนนที่ท่านคิดว่าตรงกับตัวท่านมากที่สุด

- 1 ท่านสวมใส่ และถอดอุปกรณ์พยุงนิ้วหัวแม่มือด้วยตนเองได้ยากง่ายเพียงใด?

0	5	10
ยาก		ง่าย

- 2 อุปกรณ์พยุงนิ้วหัวแม่มือทำให้ท่านเกิดความรู้สึกเจ็บปวด หรือไม่?

0	5	10
เจ็บปวดมาก		ไม่เจ็บปวดเลย

- 3 เมื่อท่านใส่อุปกรณ์พยุงนิ้วหัวแม่มือท่านสามารถใช้งานมือข้างที่ใส่อุปกรณ์พยุงนิ้วหัวแม่มือได้มากน้อยเพียงใด?

0	5	10
ใช้ไม่ได้เลย		ใช้ได้ตามปกติ

- 4 ท่านสามารถใส่อุปกรณ์พยุงนิ้วหัวแม่มือตามระยะเวลาที่แพทย์กำหนดได้หรือไม่?

0	5	10
ไม่ได้เลย		ได้ %100

- 5 ท่านคิดว่าอุปกรณ์พยุงนิ้วหัวแม่มือมีประโยชน์ต่อท่านมากน้อยเพียงใด?

0	5	10
ไม่มีประโยชน์		มีประโยชน์มาก

Concurrent validity and accuracy of wrist-wearable devices to track heart rate during exercise in sedentary individuals

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ABSTRACT

Background: Heart rate (HR) is commonly used as an indicator to represent a change in oxygen consumption and energy expenditure during activities. Nowadays, HR is easily measured by low-cost wrist-wearable devices, but a few studies examine the validity and accuracy of these devices in sedentary people.

Objective: The study aimed to explore the concurrent validity and accuracy of low-cost wrist-wearable HR devices (The GT2e: approx. 4000 THB and Red Mi watch 2 lite: approx. 1000 THB) for measuring HR during exercise on a treadmill in people with a sedentary lifestyle.

Materials and methods: Seventy-six sedentary participants (60 female; 78.95%) were instructed to wear a Polar H7 while randomly wearing a watch on each hand. Participants were asked to walk or run on the treadmill for 40 minutes, including free-living activities, exercise, and HR recovery phases. Pearson's correlation coefficient was utilized to explain the levels of correlation (concurrent validity) of wrist wearable devices with the Polar H7. In contrast, the Bland-Altman method, Concordance correlation coefficient (CCC), and Mean Absolute Percentage Error (MAPE) were then used to determine the accuracy of wrist wearable devices.

Results: The GT2e had an excellent agreement with the Polar H7 in free-living activities, exercise sessions, and the HR recovery phase (CCC=0.88, 0.85 & 0.78, respectively) and strong correlation with the criterion measured; Polar H7 ($r=0.79 - 0.88$; $p<0.001$). While Red Mi watch 2 lite also had an excellent agreement and correlation in free-living activities and the HR recovery phase (CCC=0.88 - 0.85; $r=0.79$), but a moderate agreement was found in the exercise phase (CCC=0.55; $r=0.61$ [$p<0.001$]).

Conclusion: Both the GT2e and Red Mi watch 2 lite wrist-wearable devices could be used as alternative HR-measured devices to detect HR in sedentary people's daily lives. However, the GT2e wrist-wearable device was more valid and accurate in detecting HR than the Red Mi watch 2 lite.

Introduction

Heart rate (HR) is helpful in wide areas, including clinical medical care, pervasive health care, sports, and well-being centers. It was described as a critical indicator for detecting the efficiency of cardiovascular response and heart functionality during activity and exercise.¹⁻⁴ Thus, the introduction of HR-tracking-wearable-technology devices has become a new phenomenon for consumers and removes the burden of wearing an electrocardiograph (ECG) or chest straps, which is a standard measure for HR tracking, which is not comfortable or practical in some activities.^{3,5} Hence, these consumer wrist-wearable HR

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trackers have already become popular for purchase and use.^{3,6,7}

Wrist-wearable devices have begun incorporating heart rate measures using photoplethysmography (PPG) technology: this involves flashing green LED light through the skin to detect the expansion and contraction of wrist capillaries with each pulse.⁶⁻⁸ Algorithms are then applied to estimate heart rate from that information continuously. With the expanding market in wearable activity monitors, the research community has been focused on validating the properties of PPG to detect outcomes among these devices. Several studies have demonstrated their validity and accuracy or agreement in the most famous brand and high-cost devices (i.e., Apple, Garmin, or Fitbit),^{1,6-10} but none at low-cost devices, which limits their application for clinical or research purposes.¹¹ Also, there is limited knowledge of the validity and accuracy of these low-cost devices to detect HR in sedentary individuals, whose numbers have been continuously increasing, particularly teenagers and adults (81% and 23%, respectively). WHOs reported that prolonged sitting or sedentary behaviors are linked to high risks of noncommunicable disease (NCDs) such as high blood pressure, type II diabetes, obesity, depression, or chronic heart disease.¹²

Therefore, the objective of this study is to evaluate the validity and accuracy of the heart rate estimates produced by low-cost wrist-wearable devices (<5,000 THB) compared to the gold standard (Polar H7) during treadmill training among sedentary individuals. The information summarized herein can be used to inform consumers and can aid researchers in having more options for selecting physical activity monitoring devices in study design.

Materials and methods

Participants

A sedentary adult aged 18-25 from Srinakharinwirot University participated in this cross-sectional study from March to December 2022. Recruitment was carried out via posters and leaflets within the university and through word of mouth. Each participant went through a screening survey for sedentary behavior using a questionnaire, namely the Global Physical Activity Questionnaire (GPAQ; METs <600 mins/week).¹³ The exclusion criteria were any conditions or disorders that might affect the ambulatory status—such as brain function disorders,¹⁴ musculoskeletal pain (with an intensity of pain more than 5 out of 10 on a numerical pain rating scale),¹⁵ deformities in the joints of the lower extremities, obesity (body mass index >29.9kg/m²),¹⁶ having a cardiac pacemaker or cardiovascular or lung disease,¹⁷ having tattoos around their wrists or forearms and inability to follow the research protocols of the study.³

The sample size estimation for the primary objective of the study (concurrent validity) was calculated from a pilot study (N=30), which sets the level of correlation (r) to 0.354-0.760 for each device and the α to 0.05; the findings indicated this study required 11-76 participants to obtain 90% power of the test. However, a systematic review study recommends that 50-99 participants are adequate

to minimize selection bias for the study's secondary objective; the total sample size was hence 76 participants.¹⁸ Then, eligible participants signed an informed consent document approved by the Srinakharinwirot University Ethics Committee in Human Research (SWUEC 417/2564) before participating.

Instruments

Criterion measures

The Polar H7 was selected as the gold standard for heart rate measurement in the current study.^{8,14,19} The heart rate strap was attached at the distal sternum firmly against the skin and required continuous Bluetooth connection for HR readings from the Polar Beat application. In addition, this instrument has been studied regarding the validation and accuracy, which was reported to have a high correlation and agreement with ECG.³

Wrist-wearable devices

The present study examines 2 brands of low-price (<5,000 THB) wrist wearable devices that were easily purchased in the shop. They were GT2e (Huawei Technologies Co., Ltd., approx. 4,000 THB) and the Red Mi watch 2 lite (Xiaomi Inc., approx. 1,000 THB). Each device estimates heart rate from the wrist using PPG technology, but the number of PPG is different between the devices; the GT2e has 2 PPG and photodiodes, Red Mi watch 2 lite has only 1 PPG and photodiodes. Both require Bluetooth connection for HR recording from their application. Using a simple random method, participants were randomly instructed to wear a watch on the right or left wrist. Previous studies demonstrated no difference in the accuracy of the HR monitors based on which wrist they are worn on if individuals have no vascular disease.¹ Wrist-wearable devices were fastened tightly above the ulnar styloid [GT2e and Red Mi watch 2 lite on the right-hand sides for 46 and 30 participants, respectively].

Protocol

A novice assessor was trained in the methods for administering the treadmill and all devices and then practiced processing to record the outcomes in their own application via smartphone, with practice sessions lasting 60 minutes. In addition, preliminary studies were conducted on five subjects to ensure the smooth function of the protocol.

Participants were interviewed and assessed for their demographics (i.e., age, gender, and Body Mass Index [BMI]), vital signs, and wrist circumferences to ensure no wrist was too small for the watch strap. Once all devices were on, they were instructed to lay on the bed to measure resting HR (RHR). RHR was then converted to a target HR (THR) that was set at a moderate intensity using the formula from Karvonen: $([\%Intensity \times (HR_{max} - RHR)] + RHR)$.²⁰

Exercise protocol

Participants were then asked to walk or run on the treadmill (ST 65 Digital Treadmill, Quinton, USA) over

40 minutes at different speeds (in mph) in a room with a controlled temperature of 25° Celsius. The 40-minute protocol began with the free-living activity phase; they were instructed to walk on the treadmill at self-selected speeds for 5 minutes. After the 5-minute free-living activity phase, the 30-exercise phase was started with speed increasing at 0.5 mph every 1 minute until the HR raised to their target (THR). They were instructed to walk fast or run at the same speed to maintain HR until the time was up. After completing the exercise, a 5-minute heart rate recovery phase was started with treadmill speed reduction. The treadmill speed was decreased equally every 1 minute until the speed was similar at the beginning of the session.

In all activities, participants had the option of holding or releasing the treadmill bars as they needed.

Data acquisition and processing

The heart rate data were extracted in minute-by-minute format for all devices, including the Polar heart rate strap, the GT2e, and the Red Mi watch 2 lite, from the application. HR was recorded from the three devices after 2 minutes of every session. The HR data were summed individually for each of the protocol's three sessions.

Statistical analysis

Descriptive statistics were used to explain the demographics of participants as well as the findings of the study. The Kolmogorov-Smirnov test was used to estimate the normality of the data. Pearson's correlation coefficients (r) or the Spearman rank correlation coefficients (ρ) were utilized, which depend on their normality data, to explain

the levels of correlation (concurrent validity) of both wrist-wearable devices and Polar H7. The strength of the correlation was defined as modest (r or ρ of 0.30-0.49), moderate (r or ρ =0.50-0.69), and strong (r or ρ >0.70). The levels of significant differences were set at p <0.05.²¹

Bland-Altman's analysis examined the differences between the means of measuring agreement.²² This method uncovers any tendency for the variation to change with the magnitude of the measurement. Moreover, the Concordance Correlation Coefficient (CCC) was applied to obtain a measure of agreement for each device with the Polar H7. The level of the CCC was determined as modest (CCC<0.4), moderate (CCC=0.41-0.74), and strong (CCC>0.74).²³ In addition, Individual level measurement errors were evaluated with mean absolute percent errors (MAPE), which was calculated by averaging the individual absolute percent errors (i.e., |(criterion-estimation)/criterion|). An acceptable level of accuracy is indicated by a MAPE of less than 10%, while the MAPE is more than 10% but less than 25%, and the accuracy is poor.²⁴

Results

Table 1 concludes the demographics of the participants. They were enrolled in the study and had an average age of approximately 21 years old with a BMI range of 16.23-29.73 kg/m², and most of them were female. HR data from the GT2e and the Red Mi watch 2 lite are summarized in Table 2. The Red Mi watch 2 lite underestimated HR in three protocol phases. The GT2e slightly underestimated HR in free-living activity and aerobic exercise, while it somewhat overestimated HR in HR recovery sessions.

Table 1. Demographic of participants.

Variables	N=76	Min/Max
Gender ^a (female)	60 (78.95)	-
Age ^b (years)	20.7±1.23	18/25
Weight ^b (kg)	54.68±10.89	40/90
Height ^b (cm)	162.35±6.89	151/183
Body mass index ^b (kg/m ²)	20.64±3.33	16.23-29.73
Self-selected speed ^b (m/s)	0.47±0.1	0.35-0.8
Aerobic exercise speed ^b (m/s)	2.25±0.44	1.51-3.52

Note: ^athe variable is categorized as male/female, ^bdata are presented using mean±SD.

Table 2. Average heart rate in three sessions of wrist-wearable devices and PolarH7 (N=76).

Activities	Heart rate (beats/min)		
	Polar H7	GT2e	Mi
Free living activity	102.8±11.0	102.5±10.9	100.1±11.4
Aerobic exercise activity	139.0±11.0	138.2±11.3	134.3±13.6
Heart rate recovery	117.6±9.3	118.5±8.1	115.8±9.1

Note: Mi: Red Mi watch 2 lite. All data are presented using mean±SD.

The correlations between the wrist-wearable devices and the PolarH7 were strong in the free-living activity and HR recovery phase ($p < 0.01$, Figure 1). Moreover, the

correlations in aerobic exercise sessions were also strong in the GT2e ($p < 0.01$, figure 1) but moderate in Red Mi watch 2 lite ($p < 0.01$, Figure 1).

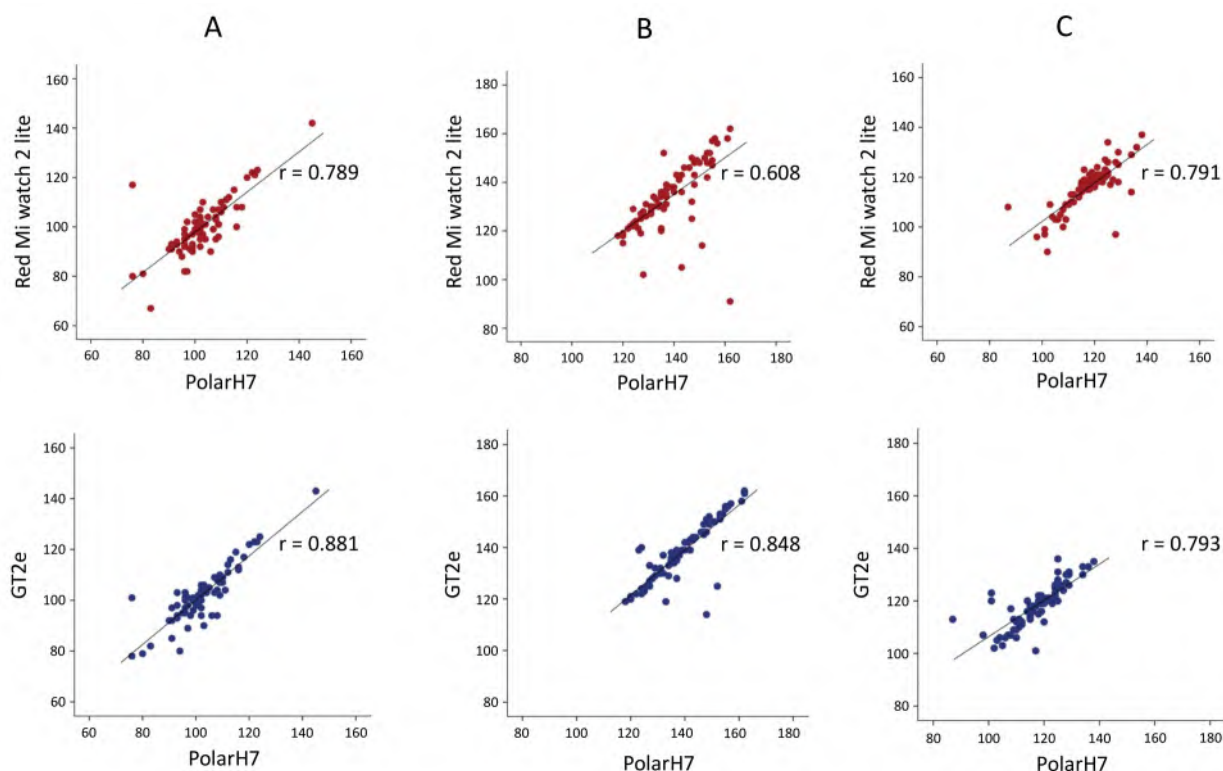


Figure 1. Scatter plot for Pearson's correlation (r) of wrist-wearable devices-measured HR with PolarH7. A: free-living activity, B: exercise, C: heart rate recovery. The top panel indicates the results for heart rate from Red Mi watch 2 lite, and the bottom panel shows the results for heart rate from GT2e separately for the three activity sessions.

The overall agreement between the GT2e and the PolarH7 on the wrist-wearable devices was high across all three sessions. Still, the CCC of Red Mi watches 2 lite was reported as having moderate accuracy in the aerobic exercise phase. Moreover, both GT2e (2.02-3.43 %) and Red Mi watch 2 lite (3.32-5.04 %) had a whole-trial MAPE,

and performance was also consistently acceptable for all three separate activities in terms of MAPE (Table 3). In the Bland-Altman plots, the data on the graph were uniformly and tightly scattered around the horizontal axis in both devices, particularly in the GT2e watch (Figure 2).

Table 3. Overall agreement data of wrist-wearable devices for heart rate estimation (N=76).

Activities	Mean diff ^a		95% LoA		MAPE	
	GT2e	Mi	GT2e	Mi	GT2e	Mi
Free living activity	- 0.32	- 2.68	-10.8 to 10.2	-16.9 to 11.60	3.43	5.04
Aerobic exercise activity	- 0.78	- 4.71	-12.8 to 11.3	-26.5 to 17.1	2.02	4.90
Heart rate recovery	- 0.96	- 1.79	-12.1 to 10.2	-13.4 to 9.8	2.70	3.32

Note: LoA: limit of agreement, MAPE: mean absolute percentage error, Mi: Red Mi watch 2 lite, ^amean difference was calculated using $\text{Mean}_{\text{wrist-wearable device}} - \text{Mean}_{\text{PolarH7}}$

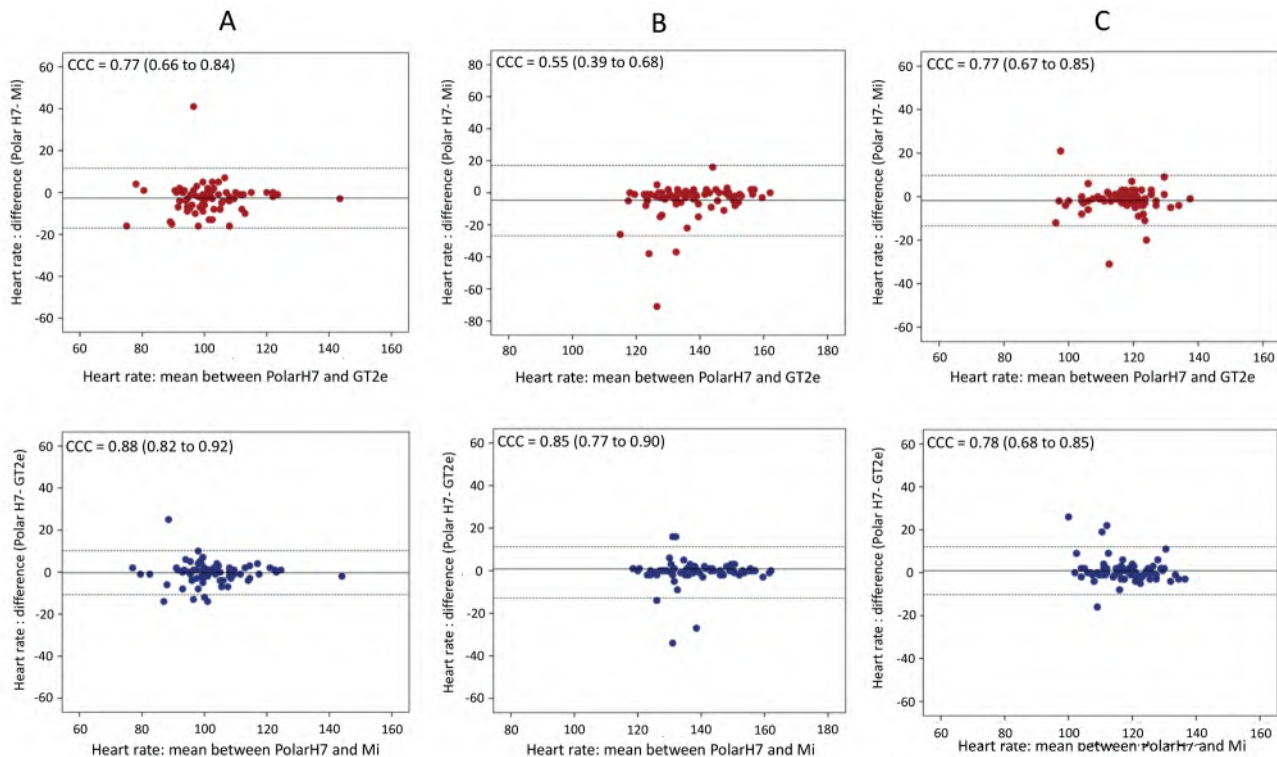


Figure 2. Concordance correlation coefficient (CCC) and Bland-Altman plots comparing heart rate between wrist-wearable devices and PolarH7. Mi: Red Mi watch 2 lite, A: free-living activity, B: exercise, C: heart rate recovery. The top panel indicates the results for heart rate from Red Mi watch 2 lite, and the bottom panel shows the results for heart rate from GT2e separately for the three activity sessions.

Discussion

The PPG in wrist-wearable devices has been known regarding the validity and accuracy of HR estimation. However, the existing evidence mostly involved the most famous and high-cost devices (i.e. Apple watch or Garmin), but none at low-cost devices such as Huawei or Xiaomi. The current findings revealed that the GT2e had high correlations to a criterion measure (PolarH7) ($r=0.79-0.88$; $p<0.01$) and highly acceptable accuracy ($CCC=0.78-0.88$; $MAPE=2.02-3.43\%$) in all phases. While Red Mi Watch 2 lite was also strongly correlated ($r=0.79$; $p<0.01$) and acceptably accurate ($CCC=0.77$; $MAPE=3.32$ and 5.04%) in only free-living activity and heart rate recovery phases, but it showed moderate correlation ($r=0.61$; $p<0.01$) and accuracy ($CCC=0.55$; $MAPE=4.9$) in exercise activity as compared to PolarH7. These findings provide precise data regarding the properties of both devices to estimate HR, which can be used as a proxy and alternative devices for HR measurement. The findings were coherent with previous studies; other studies have examined the validity of other famous and high-cost commercially available HR monitors with PPG heart rate features.^{1-3,8} In addition, a small MAPE and overall range were close to what we observed.⁵⁻¹⁰

However, the present study found that the GT2e strongly correlated with criterion measures to calculate HR in the exercise phase, but a moderate level was found in Red Mi watch 2 lite. These may be because the GT2e has the numbers of PPG and photodiodes equal to the

high-cost HR watch,¹¹ The GT2e uses two green infra-red light-emitting-diodes (LED) paired with light-sensitive photodiodes to detect the amount of blood flowing through the wrist. The Red Mi watch, 2 lite has only one red led and photodiode. The two infrared lights and photodetector used in the GT2e may help its software filter any unwanted noise, which may increase the validity and accuracy of GT2e in measuring HR. Furthermore, a previous study reported that the green light used in GT2e is more common due to its higher absorption by hemoglobin than the red light used in Red Mi watch 2 lite. This could result in a stronger signal for the HR watch to detect changes in blood flow.²⁵ In addition, the watch's morphology and PPG's position and photodiodes of GT2e are like those with high validity and accuracy (i.e., Apple watch 7 or Garmin Forerunner).^{3,18,26}

Data from the current study provide low-cost alternative devices for detecting HR in several phases of exercise. The number of PPG and photodiodes, as well as the colors of PPG used in wrist-wearable devices, should be considered before purchasing these low-cost devices, as these factors may interfere with the validity and accuracy of the HR measuring device.

Limitation

Indoor treadmill running could have different outcomes than running outside or on uneven ground. Future studies should be conducted to determine the effect of the exercise environment on HR. In addition, the

participants in the current study were allowed to either hold or release the treadmill bar during the protocol, which may affect the function of PPG and photodiodes. This information was in the same line with previous research, which reported changes in HR at exercise intensities, as arm movement which increases during high exercise intensity can interfere with data signaling.²⁷ Therefore, readers should be cautious about applying this information to other conditions of exercise that may require different arm positions such as exercise using a stationary bicycle.

Conclusion

The low-cost wrist-wearable device was a potential HR measurement in daily exercise. However, the GT2e wrist-wearable device was more valid and more accurate in detecting HR during exercise on a treadmill in sedentary people than the Red Mi watch 2 lite due to the number of PPG and photodiode and the color of PPG in the device.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

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References

- [1] Gillinov S, Etiwy M, Wang R, Blackburn G, Phelan D, Gillinov AM, et al. Variable accuracy of wearable heart rate monitors during aerobic exercise. *Med Sci Sports Exerc.* 2017; 49(8): 1697-703. doi:10.1249/mss.0000000000001284
- [2] Hunt K, Saengsuwan J. Changes in heart rate variability with respect to exercise intensity and time during treadmill running. *Biomed Eng Online.* 2018; 17(1): 128. doi:10.1186/s12938-018-0561-x
- [3] Pasadyn SR, Soudan M, Gillinov M, Houghtaling P, Phelan D, Gillinov N, et al. Accuracy of commercially available heart rate monitors in athletes: a prospective study. *Cardiovasc Diagn Ther.* 2019; 9(4): 379-85. doi:10.21037/cdt.2019.06.05
- [4] Wojtasz I, Cofta S, Czudaj P, Jaracz K, Kazmierski R. Effect of face masks on blood saturation, heart rate, and well-being indicators in health care providers working in specialized COVID-19 center. *Int J Environ Res Public Health.* 2022; 19(3). doi:10.3390/ijerph19031397
- [5] Sartor F, Gelissen J, van Dinther R, Roovers D, Papini GB, Coppola G. Wrist-worn optical and chest strap heart rate comparison in a heterogeneous sample of healthy individuals and in coronary artery disease patients. *BMC Sports Sci Med Rehabil.* 2018; 10: 10. doi:10.1186/s13102-018-0098-0
- [6] Damasceno V, Costa A, Campello M, Souza D, Gonçalves R, Campos E, Santos t. Criterion validity and accuracy of a heart rate monitor. *Hum Mov.* 2022; 23(1): 60–8.
- [7] Khushhal A, Nichols S, Evans W, Gleadall-Siddall DO, Page R, O'Doherty AF, et al. Validity and reliability of the Apple Watch for measuring heart rate during exercise. *Sports Med Int Open.* 2017; 1(6): E206-e11. doi:10.1055/s-0043-120195
- [8] Bai Y, Hibbing P, Mantis C, Welk GJ. Comparative evaluation of heart rate-based monitors: Apple Watch vs Fitbit Charge HR. *J Sports Sci.* 2018; 36(15): 1734-41. doi:10.1080/02640414.2017.1412235
- [9] Dooley EE, Golaszewski NM, Bartholomew JB. Estimating accuracy at exercise intensities: a comparative study of self-monitoring heart rate and physical activity wearable devices. *JMIR Mhealth Uhealth.* 2017; 5(3): e34. doi:10.2196/mhealth.7043
- [10] Powierza CS, Clark MD, Hughes JM, Carneiro KA, Mihalik JP. validation of a self-monitoring tool for use in exercise therapy. *Pm r.* 2017; 9(11): 1077-84. doi:10.1016/j.pmrj.2017.03.012
- [11] Nithiatthawanon T, Chaikereee N, Boonsinsukh R. Concurrent validity and accuracy of arm-wearable devices to detect heart rate during exercise: a systematic review. *J Med Health Sci.* 2023; 30(1): 79 - 103. Available from: <https://he01.tci-thaijo.org/index.php/jmhs/article/view/263324>
- [12] WHO Guidelines Approved by the Guidelines Review Committee. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization © World Health Organization 2020.; 2020.
- [13] Mengesha MM, Roba HS, Ayele BH, Beyene AS. Level of physical activity among urban adults and the socio-demographic correlates: a population-based cross-sectional study using the global physical activity questionnaire. *BMC Public Health.* 2019; 19(1): 1160. doi:10.1186/s12889-019-7465-y
- [14] Chow HW, Yang CC. Accuracy of optical heart rate sensing technology in wearable fitness trackers for young and older adults: validation and comparison study. *JMIR Mhealth Uhealth.* 2020; 8(4): e14707. doi:10.2196/14707
- [15] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs.* 2005; 14(7): 798-804.
- [16] Woo J, Leung J, Kwok T. BMI, body composition, and physical functioning in older adults. *Obesity (Silver Spring).* 2007; 15(7): 1886-94. doi:10.1038/oby.2007.223.
- [17] Thompson W, Medicine A, Gordon N, Pescatello L. ACSM's guidelines for exercise testing and prescription: Lippincott Williams & Wilkins; 2010.
- [18] Fuller D, Colwell E, Low J, Orychock K, Tobin MA, Simango B, et al. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. *JMIR Mhealth Uhealth.* 2020; 8(9): e18694. doi:10.2196/18694

- [19] Dürking P, Giessing L, Frenkel MO, Koehler K, Holmberg HC, Sperlich B. Wrist-worn wearables for monitoring heart rate and energy expenditure while sitting or performing light-to-vigorous physical activity: validation study. *JMIR Mhealth Uhealth*. 2020; 8(5): e16716. doi:10.2196/16716
- [20] Davis A, Convertino V. A comparison of heart rate methods for predicting endurance training intensity. *Med Sci Sports Exerc*. 1975; 7: 295-8.
- [21] Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg*. 2018; 126(5): 1763-8. doi:10.1213/ANE.0000000000002864
- [22] Giavarina D. Understanding bland altman analysis. *Biochem Med (Zagreb)*. 2015; 25(2): 141-51. doi:10.11613/BM.2015.015
- [23] Fleiss JL. Reliability of measurement. The design and analysis of clinical experiments. New York: Wiley; 1986. p. 1-32.
- [24] Swanson D. On the relationship among values of the same summary measure of error when it is used across multiple characteristics at the same point in time: an examination of MALPE and MAPE 1. *Review of Economics and Finance*. 2015; 5: 1-14.
- [25] Maeda Y, Sekine M, Tamura T, Moriya A, Suzuki T, Kameyama K. Comparison of reflected green light and infrared photoplethysmography. *Annu Int Conf IEEE Eng Med Biol Soc*. 2008; 2008: 2270-2. doi:10.1109/IEMBS.2008.4649649
- [26] Claes J, Buys R, Avila A, Finlay D, Kennedy A, Guldenring D, et al. Validity of heart rate measurements by the Garmin Forerunner 225 at different walking intensities. *J Med Eng Technol*. 2017; 41(6): 480-5. doi:10.1080/03091902.2017.1333166
- [27] Thomson EA, Nuss K, Comstock A, Reinwald S, Blake S, Pimentel RE, et al. Heart rate measures from the Apple Watch, Fitbit Charge HR 2, and electrocardiogram across different exercise intensities. *J Sports Sci*. 2019; 37(12): 1411-9. doi:10.1080/02640414.2018.1560644

Concurrent validity and accuracy of wrist-wearable devices to track heart rate during exercise in sedentary individuals

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ABSTRACT

Background: Heart rate (HR) is commonly used as an indicator to represent a change in oxygen consumption and energy expenditure during activities. Nowadays, HR is easily measured by low-cost wrist-wearable devices, but a few studies examine the validity and accuracy of these devices in sedentary people.

Objective: The study aimed to explore the concurrent validity and accuracy of low-cost wrist-wearable HR devices (The GT2e: approx. 4000 THB and Red Mi watch 2 lite: approx. 1000 THB) for measuring HR during exercise on a treadmill in people with a sedentary lifestyle.

Materials and methods: Seventy-six sedentary participants (60 female; 78.95%) were instructed to wear a Polar H7 while randomly wearing a watch on each hand. Participants were asked to walk or run on the treadmill for 40 minutes, including free-living activities, exercise, and HR recovery phases. Pearson's correlation coefficient was utilized to explain the levels of correlation (concurrent validity) of wrist wearable devices with the Polar H7. In contrast, the Bland-Altman method, Concordance correlation coefficient (CCC), and Mean Absolute Percentage Error (MAPE) were then used to determine the accuracy of wrist wearable devices.

Results: The GT2e had an excellent agreement with the Polar H7 in free-living activities, exercise sessions, and the HR recovery phase (CCC=0.88, 0.85 & 0.78, respectively) and strong correlation with the criterion measured; Polar H7 ($r=0.79 - 0.88$; $p<0.001$). While Red Mi watch 2 lite also had an excellent agreement and correlation in free-living activities and the HR recovery phase (CCC=0.88 - 0.85; $r=0.79$), but a moderate agreement was found in the exercise phase (CCC=0.55; $r=0.61$ [$p<0.001$]).

Conclusion: Both the GT2e and Red Mi watch 2 lite wrist-wearable devices could be used as alternative HR-measured devices to detect HR in sedentary people's daily lives. However, the GT2e wrist-wearable device was more valid and accurate in detecting HR than the Red Mi watch 2 lite.

Introduction

Heart rate (HR) is helpful in wide areas, including clinical medical care, pervasive health care, sports, and well-being centers. It was described as a critical indicator for detecting the efficiency of cardiovascular response and heart functionality during activity and exercise.¹⁻⁴ Thus, the introduction of HR-tracking-wearable-technology devices has become a new phenomenon for consumers and removes the burden of wearing an electrocardiograph (ECG) or chest straps, which is a standard measure for HR tracking, which is not comfortable or practical in some activities.^{3,5} Hence, these consumer wrist-wearable HR

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trackers have already become popular for purchase and use.^{3,6,7}

Wrist-wearable devices have begun incorporating heart rate measures using photoplethysmography (PPG) technology: this involves flashing green LED light through the skin to detect the expansion and contraction of wrist capillaries with each pulse.⁶⁻⁸ Algorithms are then applied to estimate heart rate from that information continuously. With the expanding market in wearable activity monitors, the research community has been focused on validating the properties of PPG to detect outcomes among these devices. Several studies have demonstrated their validity and accuracy or agreement in the most famous brand and high-cost devices (i.e., Apple, Garmin, or Fitbit),^{1,6-10} but none at low-cost devices, which limits their application for clinical or research purposes.¹¹ Also, there is limited knowledge of the validity and accuracy of these low-cost devices to detect HR in sedentary individuals, whose numbers have been continuously increasing, particularly teenagers and adults (81% and 23%, respectively). WHOs reported that prolonged sitting or sedentary behaviors are linked to high risks of noncommunicable disease (NCDs) such as high blood pressure, type II diabetes, obesity, depression, or chronic heart disease.¹²

Therefore, the objective of this study is to evaluate the validity and accuracy of the heart rate estimates produced by low-cost wrist-wearable devices (<5,000 THB) compared to the gold standard (Polar H7) during treadmill training among sedentary individuals. The information summarized herein can be used to inform consumers and can aid researchers in having more options for selecting physical activity monitoring devices in study design.

Materials and methods

Participants

A sedentary adult aged 18-25 from Srinakharinwirot University participated in this cross-sectional study from March to December 2022. Recruitment was carried out via posters and leaflets within the university and through word of mouth. Each participant went through a screening survey for sedentary behavior using a questionnaire, namely the Global Physical Activity Questionnaire (GPAQ; METs <600 mins/week).¹³ The exclusion criteria were any conditions or disorders that might affect the ambulatory status—such as brain function disorders,¹⁴ musculoskeletal pain (with an intensity of pain more than 5 out of 10 on a numerical pain rating scale),¹⁵ deformities in the joints of the lower extremities, obesity (body mass index >29.9kg/m²),¹⁶ having a cardiac pacemaker or cardiovascular or lung disease,¹⁷ having tattoos around their wrists or forearms and inability to follow the research protocols of the study.³

The sample size estimation for the primary objective of the study (concurrent validity) was calculated from a pilot study (N=30), which sets the level of correlation (r) to 0.354-0.760 for each device and the α to 0.05; the findings indicated this study required 11-76 participants to obtain 90% power of the test. However, a systematic review study recommends that 50-99 participants are adequate

to minimize selection bias for the study's secondary objective; the total sample size was hence 76 participants.¹⁸ Then, eligible participants signed an informed consent document approved by the Srinakharinwirot University Ethics Committee in Human Research (SWUEC 417/2564) before participating.

Instruments

Criterion measures

The Polar H7 was selected as the gold standard for heart rate measurement in the current study.^{8,14,19} The heart rate strap was attached at the distal sternum firmly against the skin and required continuous Bluetooth connection for HR readings from the Polar Beat application. In addition, this instrument has been studied regarding the validation and accuracy, which was reported to have a high correlation and agreement with ECG.³

Wrist-wearable devices

The present study examines 2 brands of low-price (<5,000 THB) wrist wearable devices that were easily purchased in the shop. They were GT2e (Huawei Technologies Co., Ltd., approx. 4,000 THB) and the Red Mi watch 2 lite (Xiaomi Inc., approx. 1,000 THB). Each device estimates heart rate from the wrist using PPG technology, but the number of PPG is different between the devices; the GT2e has 2 PPG and photodiodes, Red Mi watch 2 lite has only 1 PPG and photodiodes. Both require Bluetooth connection for HR recording from their application. Using a simple random method, participants were randomly instructed to wear a watch on the right or left wrist. Previous studies demonstrated no difference in the accuracy of the HR monitors based on which wrist they are worn on if individuals have no vascular disease.¹ Wrist-wearable devices were fastened tightly above the ulnar styloid [GT2e and Red Mi watch 2 lite on the right-hand sides for 46 and 30 participants, respectively].

Protocol

A novice assessor was trained in the methods for administering the treadmill and all devices and then practiced processing to record the outcomes in their own application via smartphone, with practice sessions lasting 60 minutes. In addition, preliminary studies were conducted on five subjects to ensure the smooth function of the protocol.

Participants were interviewed and assessed for their demographics (i.e., age, gender, and Body Mass Index [BMI]), vital signs, and wrist circumferences to ensure no wrist was too small for the watch strap. Once all devices were on, they were instructed to lay on the bed to measure resting HR (RHR). RHR was then converted to a target HR (THR) that was set at a moderate intensity using the formula from Karvonen: $([\%Intensity \times (HR_{max} - RHR)] + RHR)$.²⁰

Exercise protocol

Participants were then asked to walk or run on the treadmill (ST 65 Digital Treadmill, Quinton, USA) over

40 minutes at different speeds (in mph) in a room with a controlled temperature of 25° Celsius. The 40-minute protocol began with the free-living activity phase; they were instructed to walk on the treadmill at self-selected speeds for 5 minutes. After the 5-minute free-living activity phase, the 30-minute exercise phase was started with speed increasing at 0.5 mph every 1 minute until the HR raised to their target (THR). They were instructed to walk fast or run at the same speed to maintain HR until the time was up. After completing the exercise, a 5-minute heart rate recovery phase was started with treadmill speed reduction. The treadmill speed was decreased equally every 1 minute until the speed was similar at the beginning of the session.

In all activities, participants had the option of holding or releasing the treadmill bars as they needed.

Data acquisition and processing

The heart rate data were extracted in minute-by-minute format for all devices, including the Polar heart rate strap, the GT2e, and the Red Mi watch 2 lite, from the application. HR was recorded from the three devices after 2 minutes of every session. The HR data were summed individually for each of the protocol's three sessions.

Statistical analysis

Descriptive statistics were used to explain the demographics of participants as well as the findings of the study. The Kolmogorov-Smirnov test was used to estimate the normality of the data. Pearson's correlation coefficients (r) or the Spearman rank correlation coefficients (ρ) were utilized, which depend on their normality data, to explain

the levels of correlation (concurrent validity) of both wrist-wearable devices and Polar H7. The strength of the correlation was defined as modest (r or ρ of 0.30-0.49), moderate (r or ρ =0.50-0.69), and strong (r or ρ >0.70). The levels of significant differences were set at p <0.05.²¹

Bland-Altman's analysis examined the differences between the means of measuring agreement.²² This method uncovers any tendency for the variation to change with the magnitude of the measurement. Moreover, the Concordance Correlation Coefficient (CCC) was applied to obtain a measure of agreement for each device with the Polar H7. The level of the CCC was determined as modest (CCC<0.4), moderate (CCC=0.41-0.74), and strong (CCC>0.74).²³ In addition, Individual level measurement errors were evaluated with mean absolute percent errors (MAPE), which was calculated by averaging the individual absolute percent errors (i.e., |(criterion-estimation)/criterion|). An acceptable level of accuracy is indicated by a MAPE of less than 10%, while the MAPE is more than 10% but less than 25%, and the accuracy is poor.²⁴

Results

Table 1 concludes the demographics of the participants. They were enrolled in the study and had an average age of approximately 21 years old with a BMI range of 16.23-29.73 kg/m², and most of them were female. HR data from the GT2e and the Red Mi watch 2 lite are summarized in Table 2. The Red Mi watch 2 lite underestimated HR in three protocol phases. The GT2e slightly underestimated HR in free-living activity and aerobic exercise, while it somewhat overestimated HR in HR recovery sessions.

Table 1. Demographic of participants.

Variables	N=76	Min/Max
Gender ^a (female)	60 (78.95)	-
Age ^b (years)	20.7±1.23	18/25
Weight ^b (kg)	54.68±10.89	40/90
Height ^b (cm)	162.35±6.89	151/183
Body mass index ^b (kg/m ²)	20.64±3.33	16.23-29.73
Self-selected speed ^b (m/s)	0.47±0.1	0.35-0.8
Aerobic exercise speed ^b (m/s)	2.25±0.44	1.51-3.52

Note: ^athe variable is categorized as male/female, ^bdata are presented using mean±SD.

Table 2. Average heart rate in three sessions of wrist-wearable devices and PolarH7 (N=76).

Activities	Heart rate (beats/min)		
	Polar H7	GT2e	Mi
Free living activity	102.8±11.0	102.5±10.9	100.1±11.4
Aerobic exercise activity	139.0±11.0	138.2±11.3	134.3±13.6
Heart rate recovery	117.6±9.3	118.5±8.1	115.8±9.1

Note: Mi: Red Mi watch 2 lite. All data are presented using mean±SD.

The correlations between the wrist-wearable devices and the PolarH7 were strong in the free-living activity and HR recovery phase ($p < 0.01$, Figure 1). Moreover, the

correlations in aerobic exercise sessions were also strong in the GT2e ($p < 0.01$, figure 1) but moderate in Red Mi watch 2 lite ($p < 0.01$, Figure 1).

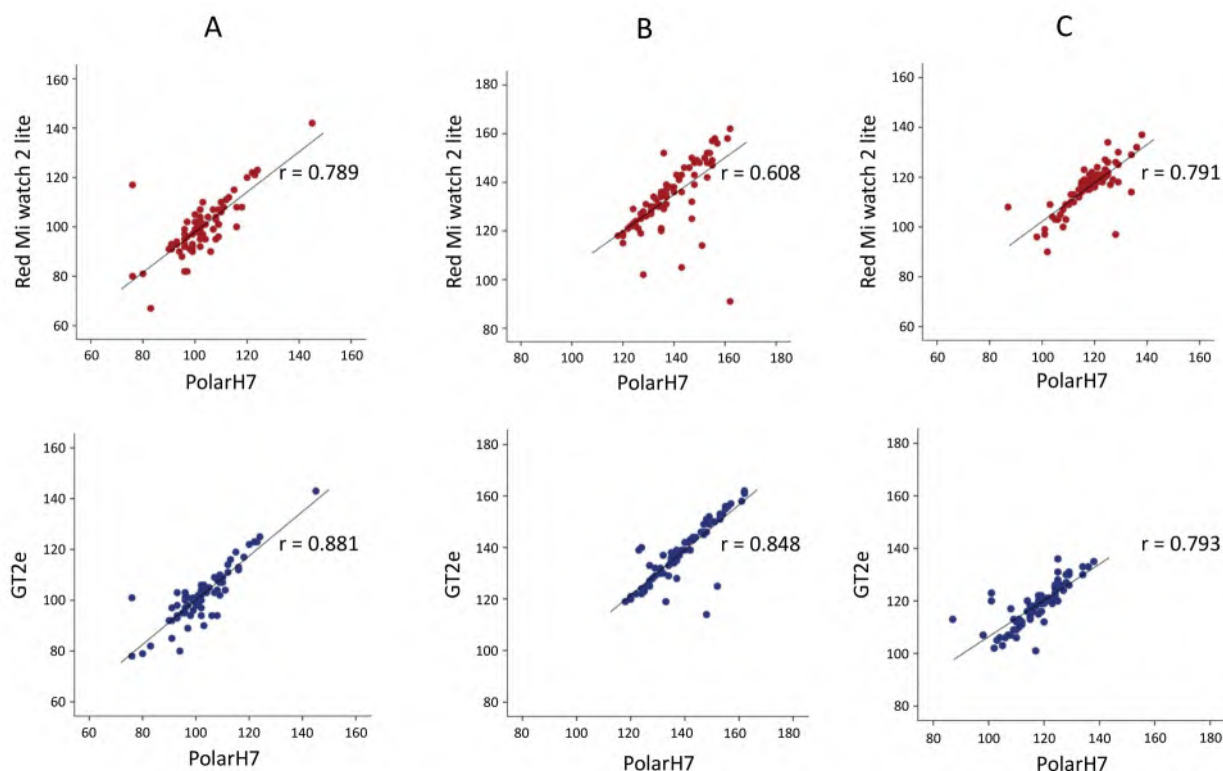


Figure 1. Scatter plot for Pearson's correlation (r) of wrist-wearable devices-measured HR with PolarH7. A: free-living activity, B: exercise, C: heart rate recovery. The top panel indicates the results for heart rate from Red Mi watch 2 lite, and the bottom panel shows the results for heart rate from GT2e separately for the three activity sessions.

The overall agreement between the GT2e and the PolarH7 was high across all three sessions. Still, the CCC of Red Mi watches 2 lite was reported as having moderate accuracy in the aerobic exercise phase. Moreover, both GT2e (2.02-3.43 %) and Red Mi watch 2 lite (3.32-5.04 %) had a whole-trial MAPE, and performance was also

consistently acceptable for all three separate activities in terms of MAPE (Table 3). In the Bland-Altman plots, the data on the graph were uniformly and tightly scattered around the horizontal axis in both devices, particularly in the GT2e watch (Figure 2).

Table 3. Overall agreement data of wrist-wearable devices for heart rate estimation (N=76).

Activities	Mean diff ^a		95% LoA		MAPE	
	GT2e	Mi	GT2e	Mi	GT2e	Mi
Free living activity	- 0.32	- 2.68	-10.8 to 10.2	-16.9 to 11.60	3.43	5.04
Aerobic exercise activity	- 0.78	- 4.71	-12.8 to 11.3	-26.5 to 17.1	2.02	4.90
Heart rate recovery	- 0.96	- 1.79	-12.1 to 10.2	-13.4 to 9.8	2.70	3.32

Note: LoA: limit of agreement, MAPE: mean absolute percentage error, Mi: Red Mi watch 2 lite, ^amean difference was calculated using $Mean_{wrist-wearable\ device} - Mean_{PolarH7}$

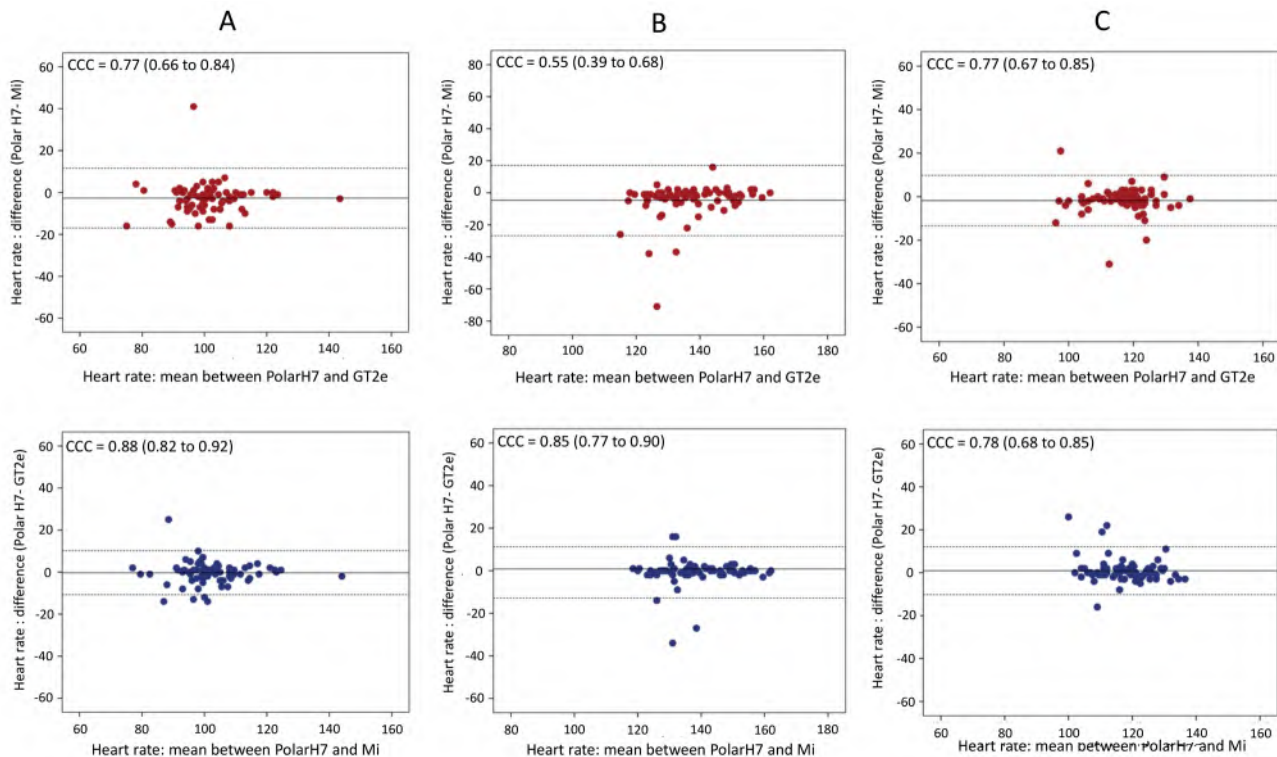


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Discussion

The PPG in wrist-wearable devices has been known regarding the validity and accuracy of HR estimation. However, the existing evidence mostly involved the most famous and high-cost devices (i.e. Apple watch or Garmin), but none at low-cost devices such as Huawei or Xiaomi. The current findings revealed that the GT2e had high correlations to a criterion measure (PolarH7) ($r=0.79-0.88$; $p<0.01$) and highly acceptable accuracy ($CCC=0.78-0.88$; $MAPE=2.02-3.43\%$) in all phases. While Red Mi Watch 2 lite was also strongly correlated ($r=0.79$; $p<0.01$) and acceptably accurate ($CCC=0.77$; $MAPE=3.32$ and 5.04%) in only free-living activity and heart rate recovery phases, but it showed moderate correlation ($r=0.61$; $p<0.01$) and accuracy ($CCC=0.55$; $MAPE=4.9$) in exercise activity as compared to PolarH7. These findings provide precise data regarding the properties of both devices to estimate HR, which can be used as a proxy and alternative devices for HR measurement. The findings were coherent with previous studies; other studies have examined the validity of other famous and high-cost commercially available HR monitors with PPG heart rate features.^{1-3,8} In addition, a small MAPE and overall range were close to what we observed.⁵⁻¹⁰

However, the present study found that the GT2e strongly correlated with criterion measures to calculate HR in the exercise phase, but a moderate level was found in Red Mi watch 2 lite. These may be because the GT2e has the numbers of PPG and photodiodes equal to the

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Data from the current study provide low-cost alternative devices for detecting HR in several phases of exercise. The number of PPG and photodiodes, as well as the colors of PPG used in wrist-wearable devices, should be considered before purchasing these low-cost devices, as these factors may interfere with the validity and accuracy of the HR measuring device.

Limitation

Indoor treadmill running could have different outcomes than running outside or on uneven ground. Future studies should be conducted to determine the effect of the exercise environment on HR. In addition, the

participants in the current study were allowed to either hold or release the treadmill bar during the protocol, which may affect the function of PPG and photodiodes. This information was in the same line with previous research, which reported changes in HR at exercise intensities, as arm movement which increases during high exercise intensity can interfere with data signaling.²⁷ Therefore, readers should be cautious about applying this information to other conditions of exercise that may require different arm positions such as exercise using a stationary bicycle.

Conclusion

The low-cost wrist-wearable device was a potential HR measurement in daily exercise. However, the GT2e wrist-wearable device was more valid and more accurate in detecting HR during exercise on a treadmill in sedentary people than the Red Mi watch 2 lite due to the number of PPG and photodiode and the color of PPG in the device.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

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References

- [1] Gillinov S, Etiwy M, Wang R, Blackburn G, Phelan D, Gillinov AM, et al. Variable accuracy of wearable heart rate monitors during aerobic exercise. *Med Sci Sports Exerc.* 2017; 49(8): 1697-703. doi:10.1249/mss.0000000000001284
- [2] Hunt K, Saengsuwan J. Changes in heart rate variability with respect to exercise intensity and time during treadmill running. *Biomed Eng Online.* 2018; 17(1): 128. doi:10.1186/s12938-018-0561-x
- [3] Pasadyn SR, Soudan M, Gillinov M, Houghtaling P, Phelan D, Gillinov N, et al. Accuracy of commercially available heart rate monitors in athletes: a prospective study. *Cardiovasc Diagn Ther.* 2019; 9(4): 379-85. doi:10.21037/cdt.2019.06.05
- [4] Wojtasz I, Cofta S, Czudaj P, Jaracz K, Kazmierski R. Effect of face masks on blood saturation, heart rate, and well-being indicators in health care providers working in specialized COVID-19 center. *Int J Environ Res Public Health.* 2022; 19(3). doi:10.3390/ijerph19031397
- [5] Sartor F, Gelissen J, van Dinther R, Roovers D, Papini GB, Coppola G. Wrist-worn optical and chest strap heart rate comparison in a heterogeneous sample of healthy individuals and in coronary artery disease patients. *BMC Sports Sci Med Rehabil.* 2018; 10: 10. doi:10.1186/s13102-018-0098-0
- [6] Damasceno V, Costa A, Campello M, Souza D, Gonçalves R, Campos E, Santos t. Criterion validity and accuracy of a heart rate monitor. *Hum Mov.* 2022; 23(1): 60–8.
- [7] Khushhal A, Nichols S, Evans W, Gleadall-Siddall DO, Page R, O'Doherty AF, et al. Validity and reliability of the Apple Watch for measuring heart rate during exercise. *Sports Med Int Open.* 2017; 1(6): E206-e11. doi:10.1055/s-0043-120195
- [8] Bai Y, Hibbing P, Mantis C, Welk GJ. Comparative evaluation of heart rate-based monitors: Apple Watch vs Fitbit Charge HR. *J Sports Sci.* 2018; 36(15): 1734-41. doi:10.1080/02640414.2017.1412235
- [9] Dooley EE, Golaszewski NM, Bartholomew JB. Estimating accuracy at exercise intensities: a comparative study of self-monitoring heart rate and physical activity wearable devices. *JMIR Mhealth Uhealth.* 2017; 5(3): e34. doi:10.2196/mhealth.7043
- [10] Powierza CS, Clark MD, Hughes JM, Carneiro KA, Mihalik JP. validation of a self-monitoring tool for use in exercise therapy. *Pm r.* 2017; 9(11): 1077-84. doi:10.1016/j.pmrj.2017.03.012
- [11] Nithiatthawanon T, Chaikereee N, Boonsinsukh R. Concurrent validity and accuracy of arm-wearable devices to detect heart rate during exercise: a systematic review. *J Med Health Sci.* 2023; 30(1): 79 - 103. Available from: <https://he01.tci-thaijo.org/index.php/jmhs/article/view/263324>
- [12] WHO Guidelines Approved by the Guidelines Review Committee. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization © World Health Organization 2020.; 2020.
- [13] Mengesha MM, Roba HS, Ayele BH, Beyene AS. Level of physical activity among urban adults and the socio-demographic correlates: a population-based cross-sectional study using the global physical activity questionnaire. *BMC Public Health.* 2019; 19(1): 1160. doi:10.1186/s12889-019-7465-y
- [14] Chow HW, Yang CC. Accuracy of optical heart rate sensing technology in wearable fitness trackers for young and older adults: validation and comparison study. *JMIR Mhealth Uhealth.* 2020; 8(4): e14707. doi:10.2196/14707
- [15] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs.* 2005; 14(7): 798-804.
- [16] Woo J, Leung J, Kwok T. BMI, body composition, and physical functioning in older adults. *Obesity (Silver Spring).* 2007; 15(7): 1886-94. doi:10.1038/oby.2007.223.
- [17] Thompson W, Medicine A, Gordon N, Pescatello L. ACSM's guidelines for exercise testing and prescription: Lippincott Williams & Wilkins; 2010.
- [18] Fuller D, Colwell E, Low J, Orychock K, Tobin MA, Simango B, et al. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. *JMIR Mhealth Uhealth.* 2020; 8(9): e18694. doi:10.2196/18694

- [19] Düking P, Giessing L, Frenkel MO, Koehler K, Holmberg HC, Sperlich B. Wrist-worn wearables for monitoring heart rate and energy expenditure while sitting or performing light-to-vigorous physical activity: validation study. *JMIR Mhealth Uhealth*. 2020; 8(5): e16716. doi:10.2196/16716
- [20] Davis A, Convertino V. A comparison of heart rate methods for predicting endurance training intensity. *Med Sci Sports Exerc*. 1975; 7: 295-8.
- [21] Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg*. 2018; 126(5): 1763-8. doi:10.1213/ANE.0000000000002864
- [22] Giavarina D. Understanding bland altman analysis. *Biochem Med (Zagreb)*. 2015; 25(2): 141-51. doi:10.11613/BM.2015.015
- [23] Fleiss JL. Reliability of measurement. The design and analysis of clinical experiments. New York: Wiley; 1986. p. 1-32.
- [24] Swanson D. On the relationship among values of the same summary measure of error when it is used across multiple characteristics at the same point in time: an examination of MALPE and MAPE 1. *Review of Economics and Finance*. 2015; 5: 1-14.
- [25] Maeda Y, Sekine M, Tamura T, Moriya A, Suzuki T, Kameyama K. Comparison of reflected green light and infrared photoplethysmography. *Annu Int Conf IEEE Eng Med Biol Soc*. 2008; 2008: 2270-2. doi:10.1109/IEMBS.2008.4649649
- [26] Claes J, Buys R, Avila A, Finlay D, Kennedy A, Guldenring D, *et al.* Validity of heart rate measurements by the Garmin Forerunner 225 at different walking intensities. *J Med Eng Technol*. 2017; 41(6): 480-5. doi:10.1080/03091902.2017.1333166
- [27] Thomson EA, Nuss K, Comstock A, Reinwald S, Blake S, Pimentel RE, *et al.* Heart rate measures from the Apple Watch, Fitbit Charge HR 2, and electrocardiogram across different exercise intensities. *J Sports Sci*. 2019; 37(12): 1411-9. doi:10.1080/02640414.2018.1560644

Diadochokinetic rate in Thai adults using between auditory-perceptual and instrumental methods

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ABSTRACT

Background: Diadochokinetic (DDK) rate refers to the time taken to execute rapid repetitive movements of articulators during speech. DDK rate assessment has been used to screen or as part of an assessment to diagnose and plan treatment for motor speech disorders. It contained alternating motion rate (AMR) and sequential motion rate (SMR) assessments. There were two main methods for DDK assessment: perceptual speech assessment and instrumental speech assessment.

Objective: This study aimed to compare the DDK rate measured by auditory-perceptual and instrumental methods and investigate the effects of age and gender on the DDK rate in normal Thai adults.

Materials and methods: In this cross-sectional study, the participants were Thai adults aged 21-78. Sixty participants were divided equally into three age groups: young adult, middle-aged adult, and older adult group. All participants were asked to repeat four speech tasks as rapidly as possible, namely, AMR as [p^ha:], [t^ha:], [k^ha:], and SMR as [p^ha:-t^ha:-k^ha:]. DDK rates were measured using two methods, namely, the auditory-perceptual method and the instrumental method, which used the Praat program. The paired sample t-test examined the difference in average DDK rates between the two methods. The one-way ANOVA was utilized to analyze the average rate differences among three age groups, while gender differences were analyzed through an independent sample t-test.

Results: The averages of SMR between the auditory-perceptual method and the Praat program were significantly different ($p < 0.05$), whereas the averages of AMR were not significantly different. The findings also found that averages of SMR had significant differences ($p < 0.05$) between three age groups and two genders. The young adult group had a higher average of SMR than middle-aged adult and older adult groups. Males had a higher average of SMR than females.

Conclusion: This result indicates that different assessment methods result in different DDK rates, especially SMR. Therefore, choosing the DDK rate assessment method should be careful and consider its accuracy. Moreover, the SMR task may be more sensitive than the AMR task to age-related change and gender factors.

Introduction

Diadochokinetic (DDK) rate refers to the time taken for rapidly repetitive movements of the articulators during speech. It has been used to screen speech problems or evaluate speech motor control or speech motor coordination skills for use as part of the diagnosis and treatment planning of motor speech disorders.¹⁻⁴ The DDK rate contained two typical assessments: alternating motion rate (AMR) and sequential motion rate (SMR). AMR was obtained by repetitions of single syllable speech rapidly, such as /pə/, /tə/, /kə/ or /pʌ/, /tʌ/, /kʌ/, etc.

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AMR considers the rapidity of syllable repetition and consistency of articulatory movement. SMR was derived from repetitions of trisyllable sounds that sequence movements of the lips, the tip of the tongue, and the base of the tongue as speedily, such as /pə-tə-kə/ or /pʌ-tʌ-kʌ/ etc. SMR is used to consider the ability to quickly and accurately switch articulators.^{1, 5-8}

Two standard DDK rate assessment methods were the auditory-perceptual and instrumental methods.^{2,4,9} The auditory-perceptual method focuses on the perception of the characteristics of speech by primarily using the assessor's ears and eyes without any equipment or special tools except voice recorders and a stopwatch with miscellaneous items such as pen and paper.^{1,2,10} The instrumental method used acoustic analysis programs¹¹ such as the Praat program,¹² the Motor Speech Profile program in the Computerized Speech Lab,¹³ or the Visi-Pitch.⁷

Concepts for evaluating speech disorders were reported that the assessor's ears and eyes are the most essential tool and the gold standard method.¹ In clinical practice, the auditory-perceptual assessment method was more popular because it cost less and was more convenient to evaluate.^{4,14} However, according to the opinions of many experienced speech-language pathologists, it is not easy to measure the DDK rate accurately and precisely, especially in patients who repeat the syllable tasks too speedily or intermittently, with low voice volume or unclear speech. As a result, it is difficult for the assessor to listen and perceive clearly during the DDK assessment.^{2,5} On the other hand, the instrumental assessment method provides a visible quantitative result.^{1,2}

Over the past two decades, many studies have been conducted to analyze the DDK rate using the Praat program because it is free, easy to access, and simple to use.^{2, 8, 15-17} Praat is a software program developed by Paul Boersma and David Weenink. It was used to analyze and reconstruct acoustic sounds. The Praat program could display the waveform or spectrogram, including pitch, intensity, formant frequency, and duration of acoustic voice and speech samples.¹²

Studies of DDK rate measurement methods have been diverse and different from the past to the present. However, the primary purpose of the studies was to obtain an accurate and optimal measurement method for measuring DDK rates.^{2,4,13,14,18} Many studies recommended instrumental measurement methods because they demonstrated clear graphs or spectrograms.^{2, 4, 13, 18} On the other hand, a survey by Fletcher found that instrumental and auditory-perceptual measurements had similar results, which was acceptable.¹⁴ Therefore, the present research compared the DDK rate between the method of measurement using the Praat program and the auditory-perceptual measurement. Moreover, gender and age factors were compared to consider the factors affecting DDK rate differences.

Methods

Study design and participants

Data was collected at the Speech Clinic in Ramathibodi Hospital between October 2021 and April 2022. The participants in this study were recruited using convenience sampling, and sixty normal Thai adults were selected from volunteers who were normal adults or relatives of patients receiving therapeutic services at Ramathibodi Hospital. The sample sizes were calculated using the GPower 3.1 program by computing the sample size of the One-Way ANOVA. Average DDK rates for each age group of the study by Chu *et al.*¹⁹ was obtained to calculate sample sizes. The sample size of each group was calculated as fifteen. Thus, the total sample size was calculated as forty-five. However, the prevention of errors in data collection was reserved. An additional 5 participants per group increased the sample size of each group. Therefore, there were sixty participants. The age range of participants was 21-78 years. They were divided into three age groups: the young adult (21-39 years old), the middle-aged adult (40-59 years old), and the older adult (60-78 years old). The three age groups had 20 participants, equal for each group. Each group had an equal number of males and females. The demographic data are shown in Appendix 1.

The inclusion criteria were Thai native speakers. They did not have any previous instances of communication disorders, neurological disorders, trauma, or surgery involving the head, neck, or chest. Additionally, there were no records of lung or respiratory diseases such as tuberculosis, pleural fibrosis, flu, or asthma that might impact speech during the data collection. Furthermore, they were non-smokers who hadn't smoked in the past five years.

The exclusion criteria were participants with issues with controlling oral movement or hearing problems that affected daily communication. They were tested for oral movement control by the voluntary movement subtest in the Apraxia Test for Thai Adults¹⁹ (Appendix 2). The hearing problems of participants were screened by the Speech Discrimination Screening Task in the Thai Adaptation of Arizona Battery for Communication Disorders of Dementia²⁰ (Appendix 3) by the researcher, a speech-language pathologist. If there were some problems, those participants were excluded. Five participants who did not meet the criteria during the data collection were excluded. However, the researcher selected additional participants who met the requirements until the total number reached sixty.

Instruments

The instruments used in this study consist of a laptop with the Audacity program, a broad program for recording speech samples,²¹ and the Praat program.¹² Moreover, a condenser microphone was plugged into the computer to record audio using the Audacity program, and a stopwatch was employed to time the speech repetitions.

Procedure

The data collection procedure was divided into two parts. The first part was collecting speech samples of DDK tasks. The second part measured the DDK rate, which involved using an auditory perceptual method and analyzing it with the Praat program.

For the first part, the researcher collected speech samples from participants individually in a quiet room. The participants were given instructions and a demonstration of the DDK test by repeating a syllable as fast as possible. The tasks consisted of repeating each of [p^ha:], [t^ha:], and [k^ha:] twenty times and then repeating a group of syllables [p^ha:-t^ha:-k^ha:] ten times.¹⁴ Each speech sample was digitally saved as a .wav file for later analysis.

For the second part, all speech sample data were measured using the auditory perceptual method. Then, they were calculated by using the Praat program. The Praat measurement method was started one month after the auditory perceptual method to reduce bias in data analysis. The researcher played back the speech samples during the evaluation using both methods. So, the researcher conducted the assessment by Praat program one month apart to avoid being able to recognize the speech sample. For the auditory perceptual method, all speech samples were heard through a loudspeaker in a quiet room and timed with a stopwatch. The speech samples were assessed using the Praat program for the instrumental method. DDK rate measurement was performed by analyzing the waveforms and spectrograms

displayed in the Praat program window. The time of the DDK rate was calculated using syllables per second.

Ethical consideration

This study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, COA. MURA2021/635 on 04 August 2021. All participants signed informed written consent forms before starting data collection.

Statistical analysis

The STATA SE-64 version 17 program categorized and analyzed the data.²² Descriptive statistics, including means and standard deviations, were calculated to describe the demographic information and DDK rate. The mean differences in DDK rate between the two methods, age groups, and gender were analyzed based on the normal distribution of sample data. A paired sample t-test was employed to compare the DDK rate differences between the two measurement methods. An independent sample t-test was used to compare the differences in DDK rate between genders. A one-way ANOVA was performed to compare the differences in DDK rate between the three age groups. The level of significance was set at 0.05.

Results

The statistical comparison results of DDK rates using two different measurement methods are presented in Table 1.

Table 1. Mean differences in DDK rates between the instrumental and perceptual methods.

Task	Method	Mean (syl./sec.)	SD	95%CI	t	p
[p ^h a:]	Instrumental	4.63	0.79	4.43-4.84	0.36	0.721
	Perceptual	4.61	0.79	4.41-4.82		
[t ^h a:]	Instrumental	4.56	0.85	4.34-4.78	- 1.06	0.296
	Perceptual	4.62	0.87	4.39-4.84		
[k ^h a:]	Instrumental	4.39	0.87	4.17-4.62	- 1.59	0.118
	Perceptual	4.47	0.90	4.23-4.70		
[p ^h a:-t ^h a:-k ^h a:]	Instrumental	5.32	1.15	5.02-5.62	- 17.07*	<0.001
	Perceptual	5.88	1.37	5.52-6.23		

*p<0.05

The analysis demonstrates that the differences between the DDK rates measured with the two methods were not statistically significant for AMR values. On the other hand, they were statistically significant for SMR at p<0.001.

In addition, the Bland-Altman method was used to determine agreement between the two quantitative measurements and to consider the difference between the two measurement methods. The results of the Bland-Altman plot are shown in Figure 1.

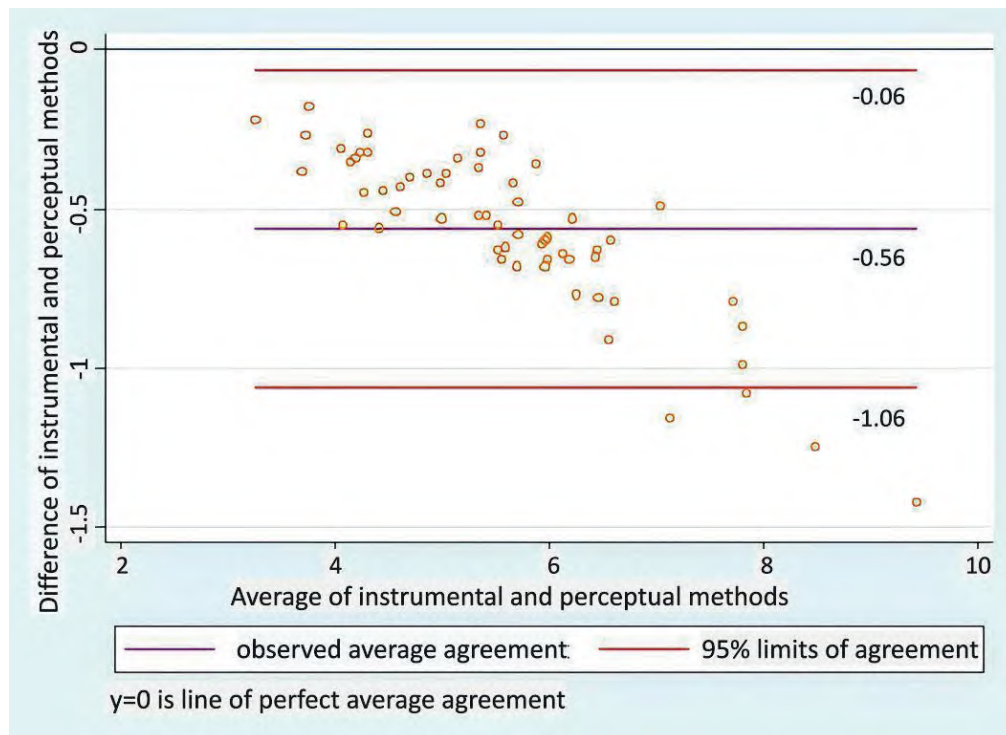


Figure 1. Bland-Altman plot analysis for $[p^h a:-t^h a:-k^h a:]$.

According to Figure 1, there was a systematic difference in SMR between the two different measurement methods. As the SMR was produced faster, the difference between the rates measured by the two methods became greater.

The results of the statistical comparison of mean DDK rates between the three age groups are presented in Table 2.

There were no statistically significant between the three age groups for AMR values. On the other hand, there was a statistically significant difference between the three age groups for only SMR at $p < 0.001$.

Then, a post-hoc Bonferroni test was used to determine the difference between SMR for three age groups by group-wise comparison in Table 3.

Table 2. Mean differences in DDK rates between age groups.

Task	Group	Mean (syl/sec)	SD	F	p
[p ^h a:]	Young	4.73	0.91	0.25	0.779
	Middle-aged	4.55	0.69		
	Older	4.62	0.79		
[t ^h a:]	Young	4.69	0.98	0.61	0.546
	Middle-aged	4.60	0.72		
	Older	4.39	0.86		
[k ^h a:]	Young	4.67	0.98	2.57	0.086
	Middle-aged	4.45	0.70		
	Older	4.07	0.84		
[p ^h a:-t ^h a:-k ^h a:]	Young	6.13	1.14	13.18*	<0.001
	Middle-aged	5.27	0.81		
	Older	4.56	0.93		

* $p < 0.05$

Table 3. A post-hoc Bonferroni test result for SMR between three age groups.

Group-wise comparison		Mean difference	p
Young	Middle-aged	0.86*	0.020
Young	Older	1.57*	<0.001
Middle-aged	Older	0.71	0.074

* $p < 0.05$

The mean SMR between the young and middle-aged adults was statistically significant at $p=0.020$. Moreover, the mean SMR rate in young adults differed significantly from that in older adults, with a $p<0.001$. The mean of SMR

indicated that the young adult group had a considerably faster rate than other groups. The differences in the DDK rates between females and males are shown in Table 4.

Table 4. Mean differences in DDK rate by gender.

Task	Gender	Mean (syl/sec)	SD	t	p
[p ^h a:]	Female	4.50	0.70	-1.27	0.209
	Male	4.76	0.86		
[t ^h a:]	Female	4.42	0.78	-1.26	0.212
	Male	4.70	0.92		
[k ^h a:]	Female	4.25	0.76	-1.32	0.193
	Male	4.54	0.96		
[p ^h a:-t ^h a:-k ^h a:]	Female	4.97	1.07	-2.43*	0.018
	Male	5.67	1.14		

* $p<0.05$

From Table 4, the DDK rate of males tends to be faster than females. However, there were no statistically significant differences in DDK rate between females and males for AMR values. On the other hand, there was a statistically significant difference in DDK rate between the two genders for SMR at $p=0.018$. The mean of SMR indicated that males had a significantly faster rate than females.

Discussion

The current study's findings indicated that the DDK rate between the perceptual and instrumental methods was different, which there was only statistically significant for SMR as [p^ha:-t^ha:-k^ha:] ($p < .05$). From the literature review, no studies compared the difference between auditory-perceptual method and instrumental method by using Praat program. Nevertheless, a study by Fletcher compared the DDK rate between using auditory perception with a stopwatch and instrumental measurement by an oscilloscope, in which oscillography displayed the DDK rate in the waveform. His study found that the DDK rates were similar between a stopwatch and an oscilloscope. He concluded that using a stopwatch could be as accurate as using instrumental measurement.¹⁴ However, this study's results were inconsistent with Fletcher's study.¹⁴ This study and Fletcher's study might be because it employed different research methodologies. Namely, the participants of this study were adults, whereas Fletcher's study was children. Moreover, both studies had different DDK tasks. This study consisted of [p^ha:], [t^ha:], [k^ha:], and [p^ha:-t^ha:-k^ha:] while the Fletcher's study comprised /pʌ/, /tʌ/, /kʌ/, /fʌ/, /lʌ/, /pʌtə/, /pʌkə/, /tʌkə/, and /pʌtəkə/. Furthermore, there was a contrast in the approach to compare the differences between DDK rate measurement methods. This study separately compared each task of DDK rate, while Fletcher's study used the total DDK rate.¹⁴

This study found a statistically significant difference between the two measurement methods for SMR. This may be because of the sound characteristics of the SMR task. It was the sequential trisyllable repetition of the bilabial-alveolar-velar sound,⁴ which was more

complex. Furthermore, the more incredible speed of the sequential trisyllable repetition might affect the more difficult auditory perception during evaluation.²³ From the result of the Bland-Altman plot in this study, the graph demonstrated a tendency for more significant differences between the Praat measurement method and the auditory-perceptual method when the SMR rate was faster. It is possible that the SMR with a more rapid rate can make it more challenging to recognize and count the repetitions of the DDK rate.²³ For the auditory-perceptual assessment method, factors affecting auditory perception, such as speed of speech and complexity, also play a role in the difficulty of listening and auditory error.^{2,4,24}

For the DDK assessment using the auditory perceptual method with a stopwatch, the uncertainty of the timekeeper's response or human error may occur, such as the speed to press the start/stop button. The timekeeper's response to the start and stop was an essential issue in the human error of using the stopwatch.²⁵ Moreover, there was a report on Gadesmann and Miller's study about the reliability of DDK rate measurement. They found that the reliability among and within raters was below the acceptable level for clinical diagnosis and outcome evaluation.² Therefore, this issue should be considered with very caution. The DDK rate assessment using the acoustic analysis instrument could prevent and reduce the occurrence of evaluation errors. The accuracy and reliability are the issues of concern in the DDK evaluation,⁴ possible problems for measuring the DDK rate should be avoided, such as human errors.² The assessment using instruments does not replace the necessity for expert clinical interpretation. However, it helps mitigate the quantification issues highlighted in this study and may enhance the effective integration of DDK tasks in evaluating motor speech disorders.² The researcher recommends that if an auditory perceptual assessment is necessary, it should be done in a quiet room, and the assessor must be prepared for the evaluation. Furthermore, there are currently a variety of acoustic analysis instruments available to evaluate DDK rates, and some of them are easy to access, have lower costs,² and

are widely used in research,^{2,15-17,26} such as the Praat free program.¹² Therefore, the acoustic analysis instrument was suggested for accuracy in the DDK assessment.²

The difference in DDK rate among the three age groups, obtained by the Praat measurement method, showed that the young adult group had higher DDK rates than the middle-aged and older adult groups. The reasons might be the change in the anatomy and physiology of speech production with age-related changes. It was reported that the young adult had a better structure and function of speech mechanism than the older adult.²⁷ Moreover, the coordination of speech movement declined with age, primarily due to decreased muscle strength and alterations in the neuromotor function of the speech mechanism.^{16,28,29}

Age-related changes in speech rate are attributed to anatomical and physiological changes in oral structure and reduced lung capacity, which can be measured by oral DDK assessment.²⁸ Nevertheless, this study found significant age-related differences only in SMR values, especially among older adults. A Thai study reported that SMR significantly decreased with age.¹⁰ For age-related changes, the SMR task may better reflect the decline in motor speech control than the AMR task. A study by Lancheros *et al.* reported that the SMR task may be more sensitive to age-related changes in oral motor abilities than the AMR task.²⁶

The different DDK rates between genders, obtained by the Praat measurement method, demonstrated that the different AMR of males had slightly faster average rates than the females as 0.26, 0.28, and 0.29 syllables per second for [p^ha:], [t^ha:], and [k^ha:]. The different SMR of males had a faster average rate than the females at 0.7 syllables per second for [p^ha:-t^ha:-k^ha:].

The tendency of the current study showed that males had a faster average rate than females for SMR and AMR. This may be because men had larger muscle fibers, stronger muscles, and greater lung size than women.³⁰⁻³² Furthermore, Bennett *et al.* studied tongue control for speech, and the SMR task was one of the speech tasks used in their study. They found that males exhibited significantly greater movement ranges of tongue body than females.³³ In addition, men's lung capacity for respiration was greater than that of women in the same age group.^{34,35} This result was consistent with the study of Pierce *et al.*,⁸ Alshahwan *et al.*,¹⁵ Topbaş *et al.*,³⁶ and John *et al.*³⁷ Those studies found that the male group's average rates of SMR and AMR tend to be faster than the female group.^{8,15,36,37} For the statistical result of this study, it was observed that SMR had significant differences between genders, whereas AMR did not demonstrate significant differences. This result was inconsistent with the resulting research of Pierce *et al.*⁸ They found that AMR was an essential difference between genders, and SMR was not significant. However, their participants were only older adults, who were 65 to 86 years old. Pierce *et al.* reported that it was unclear why the SMR was not affected by gender while the AMR was affected.⁸ From the statistical results of the SMR

in this study, it may be due to tongue movements during speech contributing to the observed gender differences. A study using electromagnetic articulography was conducted to compare SMR and AMR tasks. It found that the tongue demonstrates greater speed and range of motion during SMR than AMR.³⁸ Moreover, men showed significantly greater ranges of tongue body movement than women during the SMR task.³³

Limitations of this study

A limitation of this study was the small sample size. The DDK rate obtained in this study cannot be a normative value. Thus, future studies should collect data from a large group of normal Thai adults to establish normative data. This study considered the factors of gender and age that affect DDK rates. However, some factors may affect the DDK rate, such as the use of dentures and chronic respiratory-related conditions.

Consequently, those factors should be considered in the future. This study used only one speech and language therapist to evaluate DDK rates. Therefore, future research might investigate the inter-rater and intra-rater reliability of auditory-perceptual measurement for DDK rate assessment. Finally, the Praat program was used to measure the DDK rate in this study. However, other instruments, such as the Dr. Speech program or the Computerized Speech Lab (CSL) program, could measure DDK rates. Therefore, future studies may use such tools to compare auditory-perceptual and instrumental measurements.

Conclusion

The current study aimed to measure DDK rates using instrumental and auditory-perceptual methods. The oral DDK rates consisted of the alternating motion rate (AMR) and the sequential motion rate (SMR). The study involved 60 adults with normal speakers, evenly separated by gender and age.

The average of AMR and SMR were compared between the instrumental and the perceptual measurement methods. The results demonstrated that the differences in the SMR between the two methods were statistically significant ($p < 0.05$). Conversely, the differences in AMR were statistically non-significant. However, using instruments for DDK rate measurements, especially the SMR, should yield more accuracy and precision.

Regarding the age factor, the average DDK rate decreases from young to older adults. The comparison of the SMR of the three age groups showed significant differences ($p < 0.05$). In contrast, the differences in AMR among the three age groups were not statistically significant ($p > 0.05$).

Regarding gender factors, males tend to demonstrate faster average DDK rates than females. However, gender significantly influenced SMR.

Therefore, it is important to consider both gender and age ranges when determining or comparing normative values for DDK rates, especially SMR.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

References

- [1] Duffy JR. Motor speech disorders: substrates, differential diagnosis, and management. 3rd Ed. St. Louis, Mo: Elsevier Mosby; 2013.
- [2] Gadesmann M, Miller N. Reliability of speech diadochokinetic test measurement. *Int J Lang Commun Disord.* 2008; 43(1): 41-54. doi: 10.1080/13682820701234444.
- [3] Johnson JP, Moulton RD. Nature and treatment of articulation disorders. Springfield: Thomas; 1980.
- [4] Kent RD, Kim Y, Chen LM. Oral and laryngeal diadochokinesis across the life span: a scoping review of methods, reference data, and clinical applications. *J Speech Lang Hear Res.* 2022; 65(2): 574-623. doi: 10.1044/2021_JSLHR-21-00396.
- [5] Baken RJ, Orlikoff RF. Clinical measurement of speech and voice. San Diego: Singular Publishing; 2000.
- [6] McNeil MR. Clinical management of sensorimotor speech disorders. New York: Thieme; 2009.
- [7] Prathanee B, Thanaviratananich S, Pongjanyakul A. Oral diadochokinetic rates for normal Thai children. *Int J Lang Commun Disord.* 2003; 38(4): 417-28. doi: 10.1080/1368282031000154042.
- [8] Pierce J, Cotton S, Perry A. Alternating and sequential motion rates in older adults. *Int J Lang Commun Disord.* 2013; 48: 257-64. doi: 10.1111/1460-6984.12001.
- [9] Cohen W, Waters D, Hewlett N. DDK rates in the paediatric clinic: a methodological minefield. *Int J Lang Commun Disord.* 1998; 33 Suppl: 428-33. doi: 10.3109/13682829809179463.
- [10] Satityudhakarn P, Kripanan N, Ruamsuk S. The study of diadochokinetic rate of elderly in Nonthaburi province. *Thai J Otolaryngol Head Neck Surg.* 2022; 23(1): 17-27. Available from: <https://he02.tci-thaijo.org/index.php/rcotj/article/view/258262>
- [11] Diepeveen S, van Haaften L, Terband H, de Swart B, Maassen B. A standardized protocol for maximum repetition rate assessment in children. *Folia Phoniater Logop.* 2019; 71(5-6): 238-50. doi: 10.1159/000500305.
- [12] Boersma P, Weenink D. Praat: doing phonetics by computer [Internet]. Version 6.1.47 [updated 2021 May 21]. Available from: www.fon.hum.uva.nl/praat/.
- [13] Yang CC, Chung YM, Chi LY, Chen HH, Wang YT. Analysis of verbal diadochokinesis in normal speech using the diadochokinetic rate analysis program. *J Dent Sci.* 2011; 6(4): 221-6. doi: 10.1016/j.jds.2011.09.007.
- [14] Fletcher SG. Time-by-count measurement of diadochokinetic syllable rate. *J Speech Hear Res.* 1972; 15(4): 763-70. doi: 10.1044/jshr.1504.763.
- [15] Alshahwan MI, Cowell PE, Whiteside SP. Diadochokinetic rate in Saudi and Bahraini Arabic speakers: dialect and the influence of syllable type. *Saudi J Biol Sci.* 2020; 27(1): 303-8. doi: 10.1016/j.sjbs.2019.09.021.
- [16] Mousavi SZ, Mehri A, Nabavi D, Faraji M, Maroufizadeh S. Comparing the diadochokinetic rate in Farsi-speaking young and older adults. *Iran Rehabilitation J.* 2020; 18(1): 57-64. doi: 10.32598/irj.18.1.860.1.
- [17] Knuijt S, Kalf J, Van Engelen B, Geurts A, de Swart B. Reference values of maximum performance tests of speech production. *Int J Speech Lang Pathol.* 2019; 21(1): 56-64. doi: 10.1080/17549507.2017.1380227.
- [18] Wang YT, Kent R, Duffy J, Thomas J. Analysis of diadochokinesis in ataxic dysarthria using the Motor Speech Profile program. *Folia Phoniater Logop.* 2009; 61: 1-11. doi: 10.1159/000184539.
- [19] Sarankawin C, Khanthapsunthara K, Dechonjkit S, Tiensuwan M. The apraxia test for Thai adults: performance of subjects aged 20 to 65 years [thesis]. Bangkok: Mahidol University; 2002.
- [20] Treekittichai A. The comparison of communication performance of normal elderly and young adults on the Thai adaptation of the Arizona Battery for Communication Disorders of Dementia [thesis]. Bangkok: Mahidol University; 2001.
- [21] Audacity Team. Audacity [Internet]. [updated 2021 July 23]. Available from: <https://www.audacityteam.org/>.
- [22] StataCorp. 2021. Stata: release 17. Statistical software. College station, TX: StataCorp LLC.
- [23] Smiljanić R, Bradlow AR. Speaking and hearing clearly: talker and listener factors in speaking style changes. *Lang Linguist Compass.* 2009; 3(1): 236-64. doi: 10.1111/j.1749-818X.2008.00112.x.
- [24] Kent RD. Hearing and believing. *Am J Speech Lang Pathol.* 1996; 5(3): 7-23. doi: 10.1044/1058-0360.0503.07.
- [25] Gust JC, Graham RB, Lombardi MA. Stopwatch and timer calibrations. Gaithersburg, MD: National Institute of Standards and Technology, 2009.
- [26] Lancheros M, Friedrichs D, Laganaro M. What do differences between alternating and sequential diadochokinetic tasks tell us about the development of oromotor skills? an insight from childhood to adulthood. *Brain Sci.* 2023; 13(4): 655. doi: 10.3390/brainsci13040655.
- [27] Devadiga DN, Bhat JS. Oral diadochokinetic rate - an insight into speech motor control. *Int J Adv Res.* 2012; 1(1): 10-4.
- [28] Chu SY, Lee J, Barlow SM, Ben-David B, Lim KX, Foong JH. Oral-diadochokinetic rates among healthy Malaysian-Mandarin speakers: a cross linguistic comparison. *Int J Speech Lang Pathol.* 2021; 23(4): 419-29. doi: 10.1080/17549507.2020.1808701.
- [29] Tafiadis D, Zarokanellou V, Prentza A, Voniati L, Ziavra N. Diadochokinetic rates in healthy young and elderly Greek-speaking adults: the effect of types of stimuli. *Int J Lang Commun Disord.* 2022; 57(5): 1085-97. doi: 10.1111/1460-6984.12747.
- [30] Nicholson KG, Kimura D. Sex differences for speech and manual skill. *Percept Mot Skills.* 1996; 82(1):

- 3-13. doi: 10.2466/pms.1996.82.1.3.
- [31] Nuzzo JL. Narrative review of sex differences in muscle strength, endurance, activation, size, fiber type, and strength training participation rates, preferences, motivations, injuries, and neuromuscular adaptations. *J Strength Cond Res.* 2023; 37(2): 494-536. doi: 10.1519/JSC.0000000000004329
- [32] Lutfi MF. The physiological basis and clinical significance of lung volume measurements. *Multidiscip Respir Med.* 2017; 12(1): 3. doi: 10.1186/s40248-017-0084-5
- [33] Bennett JW, Van Lieshout PH, Steele CM. Tongue control for speech and swallowing in healthy younger and older subjects. *Int J Orofacial Myology.* 2007; 33: 5-18. doi: 10.52010/ijom.2007.33.1.1.
- [34] Needham CD, Mary CR, McDonald I. Normal standards for lung volumes, intrapulmonary gas-mixing, and maximum breathing capacity. *Thorax.* 1954;9(4):313. doi: 10.1136/thx.9.4.313.
- [35] LoMauro A, Aliverti A. Sex differences in respiratory function. *Breathe.* 2018; 14(2): 131-40. doi: 10.1183/20734735.000318.
- [36] Topbaş O, Orlikoff RF, St Louis KO. The effect of syllable repetition rate on vocal characteristics. *J Commun Disord.* 2012; 45(3): 173-80. doi: 10.1016/j.jcomdis.2012.02.001.
- [37] John J, Ganapathy K, John S, Rajashekhar B. Normative for motor speech profile in Kannada-speaking adults. *J Voice.* 2014; 28(1): 7-13. doi: 10.1016/j.jvoice.2013.06.009
- [38] Berry JJ, Palahniuk S, Isaksson E, Romenesko M. Articulatory kinematics of alternating and sequential motion rate diadochokinesis [Internet]. 2014 [cited 2024 July 22]. Available from: https://epublications.marquette.edu/spaud_fac/38.

Appendix 1. Demographic data

Group	Gender	N	Age (years)	
			Mean (SD)	Range
Young adult	Males	10	28.7 (6.88)	21-38
	Females	10	31.3 (3.74)	25-38
	Both	20	30 (5.55)	21-38
Middle-aged adult	Males	10	47.4 (5.78)	40-56
	Females	10	52.1 (5.86)	42-59
	Both	20	49.75 (6.15)	40-59
Older adult	Males	10	67 (5.12)	60-78
	Females	10	64.6 (5.27)	60-74
	Both	20	65.8 (5.21)	60-78
Overall	Males	30	47.7 (16.92)	21-78
	Females	30	49.3 (14.79)	25-74
	Both	60	48.5 (15.78)	21-78

Appendix 2. Oral movement control by the voluntary movement subtest in the apraxia test for Thai adults

แบบประเมินการเคลื่อนไหวอวัยวะที่เกี่ยวข้องกับการพูด

รหัส ____

วันที่บันทึกข้อมูล วันที่ ____ เดือน ____ ปี พ.ศ. ____

	ความถูกต้อง (precise)			ความเร็ว (speed)			ความแข็งแรง (strength)		
	ถูกต้อง	ถูกบางส่วน	ไม่ถูก	ได้ทันที	ทำได้ช้า	ทำไม่ได้	แข็งแรง	อ่อนแรงเล็กน้อย	ไม่แข็งแรง
แลบลิ้นยาว									
ห่อปากกลม									
เคาะลิ้น									
แลบลิ้น เข้า-ออก									
ยิงฟัน									
ยกลิ้น แตะจมูก									
ทำแก้มป้อง									
ส่ายลิ้น ซ้าย-ขวา									

☐ ผ่าน ☐ ไม่ผ่าน

ผู้เก็บข้อมูล

Appendix 3. The speech discrimination screening task

แบบคัดกรองการประเมินการฟัง

รหัส ____ วันที่บันทึกข้อมูล วันที่ ____ เดือน ____ ปี พ.ศ. ____

การคัดกรองการฟังแยกเสียง				การแยกคู่คำ		การพูดตามคำ	
คะแนน 1 หรือ 0							
0.5 หรือ 1							
0.5 หรือ 1							
ตัวอย่าง	แนบ	แลบ	(แตกต่าง)				
1	แบ	เด	(แตกต่าง)				
2	พาด	ฟาด	(แตกต่าง)				
3	ห่ม	ห่ม	(เหมือน)				
4	ทิน	ชิน	(แตกต่าง)				
5	ฉาบ	ฉาบ	(เหมือน)				
6	ชีพ	จิบ	(แตกต่าง)				
7	เก็บ	เก็บ	(เหมือน)				
8	เต	เท	(แตกต่าง)				
9	เทา	เทา	(เหมือน)				
10	ชิบ	ชิบ	(เหมือน)				
11	กำ	กำ	(เหมือน)				
12	เวทย์	เวทย์	(เหมือน)				
13	บัตร	ผิด	(แตกต่าง)				
14	หอบ	หอบ	(เหมือน)				
15	โหวต	โบสถ์	(แตกต่าง)				
16	ชิด	ชิด	(เหมือน)				
17	สอย	ฝอย	(แตกต่าง)				
18	ว้าย	ว้าย	(เหมือน)				
คะแนนรวม = 18							

☐ ผ่าน ☐ ไม่ผ่าน (ตอบผิด 5 ข้อขึ้นไป)

ผู้เก็บข้อมูล



Exploring the role of the vestibular system in visuospatial memory in developmental dyslexia: Narrative review

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ABSTRACT

Individuals with dyslexia face significant challenges when it comes to writing and reading, even though they can receive an education. Various theories suggest that difficulties in processing auditory and visual cues, crucial for reading, are the underlying cause of developmental dyslexia. The vestibular system intricately processes the visuospatial memory, essential to reading comprehension. This review aims to provide a detailed explanation of the crucial role of the vestibular system in visuospatial memory, cognition, and motor planning.

Introduction

Developmental dyslexia is a condition marked by challenges in learning to decode and spelling skills. The DSM5 categorizes dyslexia as one type of neurodevelopmental disorder.¹ The nature and meaning of dyslexia have been controversial since its initial identification in the late nineteenth century.² Despite the abundance of scientific information concerning dyslexia, there is still an ongoing debate regarding its precise definition.^{3,4}

The National Institute of Child Health and Human Development (NICHD) has established a widely accepted definition of dyslexia, which is as follows: "dyslexia is a specific learning disability that is neurological in origin. Difficulties with accurate and fluent word recognition and poor spelling and decoding abilities characterize it. These difficulties are typically caused by a deficit in the phonological component of language, which is often unexpected for other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede the growth of vocabulary and background knowledge."⁵

Dyslexia, a prevalent learning disorder, impacts a substantial proportion of the population, with prevalence estimates ranging from 5% to 17.5%. Several factors contribute to the variation in estimates. The utilization of different operational definitions of dyslexia across various studies can result in divergent prevalence rates. For example, some studies may use more inclusive or exclusive criteria for dyslexia diagnosis. Additionally, environmental variables such as geographical regions and socioeconomic status can influence the prevalence of dyslexia in different populations.⁶ A recent comprehensive analysis revealed that developmental dyslexia affects an estimated 7% of the global population. Furthermore, the study showed a

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higher incidence of dyslexia in boys compared to girls.⁷ The processing speed, while slower and more variable in males, highlights the unique journey of overcoming challenges in developmental dyslexia, encouraging resilience and growth.⁸

Dyslexia is a chronic condition that manifests differently in each individual, depending on their specific skills and the context in which they are learning.^{4,9} Phonological processing is a fundamental component of reading proficiency. This process encompasses identifying and differentiating various speech sounds, essential for adequate speech comprehension. Furthermore, it facilitates the accurate production of sounds during verbal expression. Challenges in phonological processing are the primary cause of dyslexia, which affects an individual's oral language sound recognition and impedes their speech, reading, and spelling abilities.¹⁰ Dyslexia presents a diverse range of characteristics in the individuals it affects. Throughout the developmental trajectory spanning from childhood to adulthood, individuals with dyslexia experience diverse manifestations of challenges. During the early stages of childhood, many individuals encounter difficulties in connecting the sounds they hear to the letters they see. This foundational skill is crucial for their literacy development. As they progress and grow older, they often face more complex challenges, such as reading fluency, where they may struggle to read smoothly.¹¹

The literature has proposed numerous theories to explain the underlying causes of dyslexia. Among these theories, the phonological impairment hypothesis is the most prominent explanation for this disorder.^{1,12} Some literature suggests that issues in the cerebellum may cause dyslexia. Moreover, the connection between the cerebellum and proficient reading and mathematical aptitude is fascinating.¹³⁻¹⁵ Studies have revealed that children with dyslexia exhibit a visual attention impairment and an aberrant oculomotor pattern.¹⁶⁻¹⁸ Drawing from various theories, numerous researchers have devised diverse training methods to enhance the reading capabilities of children diagnosed with dyslexia. This review aims to thoroughly comprehend the vestibular system's role in visuospatial memory in developmental dyslexia. Specifically, it will explore the significance of the vestibular system in enhancing visuospatial skills and its potential impact on individuals with developmental dyslexia.

Timeline of developmental dyslexia

The timeline of developmental dyslexia begins with scientists exploring the possibility of learning disabilities and dyslexia as phenomena in the mid-1800s. Initially, people referred to dyslexia as "word blindness", meaning that the person cannot recognize and understand the words he sees. In 1877, Adolf Kussmaul changed the terminology of "word blindness" to "complete text blindness".¹⁹ The American medical practitioner Samuel Orton (1879-1948) conducted observations that revealed common linguistic challenges experienced by numerous children. These included difficulties distinguishing between

the letters p and q, b, and d, a strong inclination for confusing palindromic words, and a notable capacity to read from a mirror. Dr. Orton's research, which involved the study of over three thousand individuals facing language-related impediments, culminated in the identification of these difficulties as "strephosymbolia", a term denoting "twisted symbols."²⁰ In 1968, the World Federation of Neurology (WFN) provided the following definition for dyslexia: "A disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and sociocultural opportunity". However, some have criticized this definition as an "exclusion definition," arguing that it could potentially exclude underprivileged individuals or those with low IQs from receiving a dyslexia diagnosis. The Italian scientist Paulesu led a study that looked at dyslexia in people from different cultures and found that the cognitive and biological factors that cause it are the same across all of them.²¹

The term "dyslexia" was first used by Dr. Rudolph Berlin in 1887. It was first defined by Lyon in 1994 and then updated in 2002 to say that it is "a specific learning disorder that is neurobiological in origin and is characterized by difficulties with accurate and fluent word recognition and poor spelling and decoding abilities".^{22,23} Before the mid-20th century, the dominant understanding of developmental dyslexia was that it was a hereditary deficit that hindered an individual's capacity to comprehend written language visually. In the 1980s, researchers rejected this hypothesis. The brain's abnormal visual processing and failure to acquire phonological skills have revised it to a language disorder.¹²

In their summary of dyslexia, Peterson and Pennington found it moderately heritable. They also identified candidate genes involved in brain development and highlighted environmental risk factors linked to lower socioeconomic status. They noted common comorbidities like attention-deficit/hyperactivity disorder, speech/language disorders, and other learning disabilities, all influenced by shared risk factors.²⁴

Utilizing advanced brain scanning techniques and analyses, it was indicated that dyslexia is a brain-based and neurodevelopmental disorder, multifactorial and universal.^{25,26} Contemporary eye-tracking techniques have yielded valuable knowledge about the operation of the dyslexic brain while reading. These methods can effectively assess the cognitive load experienced by individuals while reading. Furthermore, they serve as a strong foundation for developing predictive and automated models instrumental in screening for dyslexia.²⁷ Moreover, eye-tracking and text-reading tasks effectively identify dyslexia and other disorders.²⁸

Neural pathways of reading

The development of reading skills encompasses several components, including reading speed, fluency, and automaticity.²⁹ Functional imaging studies prove that recognizing words proficiently relies on an organized cortical system that integrates the processing of orthographic, phonological, and lexico-semantic

aspects of words.^{30,31} Three primary interrelated systems, orthography, phonology, and semantics, enhance the reading process. These systems involve specific regions of the brain, including the occipitotemporal, temporoparietal, and inferior frontal cortex.^{29,31}

Three cortical areas consistently emerge as hubs of the reading network: the left inferior frontal gyrus (IFG), left occipitotemporal (OT) cortex, and left temporoparietal cortex (TP). The left inferior frontal gyrus (IFG) is a brain region essential for language processing and production. This region overlaps with Broca's area, which has long been associated with language production. Activation of the left IFG occurs early in the reading process and understanding of words, indicating its involvement in early phonological processing, which is the recognition and processing of the sounds of words. This early activation suggests that the left IFG plays a critical role in the initial stages of language processing.^{29,32}

The left occipitotemporal (OT) region comprises the lingual gyrus and fusiform gyrus, which are involved in word recognition. Researchers have linked the activation of the left lingual gyrus, also known as the medial OT gyrus, to the visual perception of the length of words.³³ The left temporal gyri (TP) areas involved in reading include the supramarginal gyrus (SMG), angular gyrus (AG), and posterior regions of the middle and superior temporal gyri (MTG/STG).³⁴ The SMG performs functions related to both orthographic and phonological processing, whereas the AG is primarily involved in phonological processing and semantics. The STG overlaps with Wernicke's area, which involves language comprehension and reading-related processes. The left thalamus frequently exhibits activation during reading activities, although it is typically not considered a component of the reading network.³²

Reading tasks consistently engage the cerebellum, despite its rare inclusion within the conventional reading network. The right crus connects with regions in the left hemisphere, and there are distinct functional and structural differences between typical readers and readers with developmental dyslexia (DD).¹³ The cortical reading network comprises the dorsal and ventral reading pathways. The dorsal reading pathway, consisting of the TP regions (left STG, AG, SMG) and the IFG, primarily facilitates the deciphering of words. The dorsal reading pathway overlaps with the dorsal visual pathway. The ventral reading pathway includes OT regions such as the VWFA, the MTG, and the IFG. It is associated with rapid recognition of whole words, usually familiar sight words that do not need to be decoded. Reading acquisition gradually shifts with increasing reading skills from the dorsal to the ventral pathway.^{35,36}

Theories of developmental dyslexia

There are three categories of theories related to developmental dyslexia. They are psychological, signal-processing, and neurological. The dominant psychological theory of dyslexia is phonological theory, and it hypothesizes that dyslexic children fail to acquire the skill of phonemic awareness, which is responsible

for competent reading.³⁷ Reading involves memory for phonological sequences and word retrieval, which children with dyslexia find challenging. Abnormalities in the left inferior frontal, parietal-temporal, and inferior temporal-occipital areas are linked to the phonological processing deficiency.^{38,39} The phonological deficit theory is the most often used explanation of dyslexia, yet not all dyslexics have phonological processing problems because developmental dyslexia is a multifactorial disorder.⁴⁰

The double-deficit approach is otherwise called signal processing theory for developmental dyslexia. It examines phonological and rapid-naming deficiencies in information processing. In 1974, Martha Denckla discovered that dyslexic individuals have slowness at rapid automatized naming (RAN), which is a speech timing and fluency problem.⁴¹ Maryanne Wolf later introduced the 'double deficit' hypothesis, which suggests that individuals with dyslexia have a deficit in both phonological and rapid serial/automatized naming skills. The double-deficit theory, an extension of the dominant phonological deficit theory, proposes that dyslexic individuals have a single deficit in one or a double deficit in both skills.^{37,41-43}

People with dyslexia may have a shorter visual attention span, making reading sluggish and inaccurate. In addition, they might experience visual stress, which is a condition that can be uncomfortable when they are exposed to high contrast, coarse black and white stripes. There is a high probability that this results from an excessive stimulation of the magnocellular timing system, which is accountable for rapidly signaling moments when visual events occur.⁴⁴

A recently developed set of neurological theories explores the various brain structures involved in developmental dyslexia. The magnocellular and cerebellar theories are significant in neurological theory as they provide insights into the functions and dysfunctions of the magnocellular and cerebellar pathways in the brain, contributing to our understanding of various neurological conditions and cognitive processes. According to the magnocellular theory, the visual magnocellular neurons play a crucial role in quickly processing visual attention.³⁷ Neuroimaging studies have demonstrated that irregularities in the magnocellular layers of the lateral geniculate nucleus result in atypical binocular control and visuospatial attention.³⁹

Even though more evidence supports the magnocellular theory, it does not compete with phonological theory for three reasons: 1) any dyslexics can learn to read well despite poor magnocellular function and without visual problems, 2) the dorsal attentional and visuomotor pathways are not strictly composed of magnocellular characteristics, and 3) the preponderance of evidence was correlational, indicating that a conclusive cause-and-effect relationship could not be firmly established.³⁷ A cerebellar deficit hypothesis suggests that the cerebellum plays a significant role in retrieving words from semantic memory and, thus, in decoding performance due to its connections with the dorsal and ventral reading pathways. Dysfunction in the cerebellum

may raise the likelihood of experiencing developmental reading disorders.¹⁴ According to numerous theories, dyslexia is believed to arise from a chain of impairments that stem from a singular “core deficit”. Proficient reading necessitates swift communication among a dispersed network of visual, auditory, and language processing systems. Any impairment in these systems could result in challenges when acquiring a sophisticated skill such as reading. To address the challenges associated with dyslexia, it is essential to utilize a multiple-model system. This approach can help prevent the overprediction that often occurs when relying solely on a single deficit model.⁴⁰

The significance of visual working memory and visual-spatial abilities in the reading process

The relationship between visual-spatial skills and reading abilities is a subject of ongoing debate. Visual-spatial ability encompasses a complex cognitive skill set, incorporating spatial perception, visualization, and mental rotation. The functions encompass mental imagery, navigation, distance and depth perception, and visuospatial construction, and they represent the brain’s highest level of visual processing and rely on the proper functioning of the parietal cortex, a region of the brain responsible for integrating sensory information.⁴⁵

Reading entails a range of cognitive processes, including the visual recognition of word forms and eye movements. Fixations and saccades are two types of eye movements utilized to extract visual information from text. These processes activate phonological, syntactic, and semantic information, enabling readers to access their mental lexicon and comprehend the text. Working memory (WM) significantly influences these cognitive processes, and disparities in WM capacity among individuals can predict their reading ability.⁴⁶ Working memory is an executive controller that interacts with distinct short-term storage systems for auditory-verbal and visuospatial information, in line with the multi-component model. In 1974, Baddeley and Hitch put forth a multicomponent working memory model. This model proposes the existence of an attentional controller known as the central executive, along with two subsystems: the visuo-spatial sketchpad, responsible for visual storage and processing, and the phonological loop, accountable for handling acoustic and verbal information.⁴⁷

The phonological loop and the visuospatial sketchpad are components of Visual Working Memory (VWM) and are linked to long-term memory via the episodic buffer. The episodic buffer is the intermediary between working memory (WM) and long-term memory. The study conducted by Pham and Hasson (2014) examined the components of working memory in the reading process and found that visual working memory plays a crucial role in reading comprehension. The study revealed that VWM capacity notably impacted reading fluency during the initial reading performance. However, it did not have a significant influence on the rate of change over time.⁴⁸ VWM measures are strongly linked to EWM, and the first reading represented a new and challenging task

that required participants to use their executive cognitive abilities.⁴⁹

The academic performance of primary school students is indirectly influenced by their visuospatial memory, which acts as a mediator for their arithmetic and reading abilities. Neuroimaging studies have indicated that the neural circuits in the brain’s left hemisphere support the process of converting graphemes to phonemes in alphabetic writing systems.⁵⁰ Conversely, the right hemisphere is responsible for visuospatial processing.^{47,49} Franceschini *et al.* found that visual-spatial attention influences learning to read. Poor readers made more errors on visual search tasks and didn’t benefit from valid spatial cues.⁵¹

Visuospatial and visual working memory are essential for reading and writing. An individual’s visual working memory capacity and effectiveness in transferring information to long-term memory uniquely contribute to the variations in learning abilities among individuals.

Role of visuospatial memory in developmental dyslexia

Recent updates to the reading model propose that not only the phonological system deficit but also an executive function deficit is a contributing factor in developmental dyslexia. This executive function encompasses working memory and cognitive flexibility, suggesting that these mental processes play a crucial role in dyslexia. So, dyslexia is considered a multifactorial disorder.⁵²

Visual attention impairment significantly contributes to the reading challenges in individuals with developmental dyslexia.⁵³ According to a study conducted by Taran *et al.* in 2022, it was indicated that the brain regions associated with visual attention have a significant impact on the reading abilities of individuals with dyslexia as well as those without dyslexia.⁵² This suggests that visual attention plays a crucial role in reading and may have implications for understanding and addressing reading difficulties. In the initial phases of education, complex visuospatial abilities are essential for recognizing letters and words. In instances of developmental dyslexia, a deficit in these abilities can disrupt academic achievement. Furthermore, during subsequent educational phases, broader perceptual impairments may impede the reading abilities of children with DD.⁵⁴

Working memory is an essential determinant of learning and accounts for differences in reading and writing abilities among elementary school children. In a long-term study, it was observed that there was a strong connection between verbal and visual-spatial working memory and word reading accuracy in the first and second grades. However, as the students progressed to fifth grade, none of the measures of working memory showed any significant correlation with word reading accuracy.⁵⁵ In a meta-analysis, verbal working memory had a stronger correlation with reading than visuospatial working memory, specifically after the third grade. The relationship between working memory and word recognition was more substantial than between working memory and nonword reading.^{56,57}

Individuals diagnosed with dyslexia may exhibit heightened global visual-spatial processing abilities, enabling them to perceive impossible figures more quickly and accurately than those without the condition. Notably, research indicates that individuals with dyslexia may harbor additional talents extending beyond rapid global visual-spatial processing. These findings have significant implications for developing more targeted educational strategies and career guidance tailored to capitalize on the strengths of individuals with dyslexia.⁵⁸ A study carried out by researchers at Haskins explored the cognitive and neural underpinnings of visuospatial processing abilities in adolescents with dyslexia in comparison to their typically developing peers. The research findings revealed that individuals with dyslexia demonstrated a visuospatial processing advantage, manifested as reduced response times and comparable accuracy levels when performing a task involving the processing of geometric figures.

The initial stages of word processing rely on verbal and visuospatial working memory. When this process encounters difficulties, the brain may employ visuospatial skills as a compensatory mechanism, enhancing individual learning. However, it does not necessarily contribute to improving the reading process. Consequently, strategies aimed at coordinating verbal and visuospatial skills during the early stages can aid children with dyslexia in enhancing their reading abilities.

Significance of the vestibular system in visuospatial memory

Maintaining the body's equilibrium in the gravitational field is the primary function of the vestibular system. For gaze and postural stability, it is necessary to integrate multiple sensory systems, including vestibulo-ocular tracts, vestibulo-colic tracts, and vestibulo-spinal tracts.⁵⁹ The vestibular system comprises two types of sensors: the saccule and utricle, referred to as otolith organs, responsible for sensing linear acceleration, and the three semicircular canals, which detect angular acceleration in three different planes. When functioning correctly, it integrates subconsciously with vision, proprioception, and other sensory functions to create a seamless motion experience.⁶⁰

In 1988, Levinson conducted a study exploring the vestibular system's significance in learning disabilities. He posited that the cerebellar-vestibular system is crucial in coordinating peripheral and central vision, potentially responsible for the limited perceptual span or tunnel vision. Lastly, he proposed the cerebello-vestibular basis of the learning disability hypothesis.⁶¹ Typically, normal children showed better stability in eye movements when fixating on small targets, as well as greater vergence amplitudes and less fixation instability than dyslexic children.

Various literature suggests that the normal development of cognition and learning depends upon the functional vestibular system.⁶¹⁻⁶⁴ A 2008 study by Franco and Panhoca found that children exhibiting poor academic performance demonstrated a greater chance

of experiencing vestibular dysfunction.⁶² This dysfunction is linked to cognitive functions such as visuospatial ability, attention, executive function, and memory. It may cause atrophy in the cortical vestibular network, including the hippocampus, leading to impaired memory and visuospatial ability. Additionally, more attentional resources are required to overcome postural instability after vestibular dysfunction, potentially reducing resources for cognitive tasks.⁶³

The alternate smooth-pursuit, saccadic eye movements, and fixations are essential for visual motor skills and influence reading and writing. The vestibulo-ocular reflex is responsible for eye movement while moving our head. The integration of ocular and vestibular interconnections is required not only for saccadic and pursuit but also for visual monitoring and performance concentration activities. Based on current evidence, it has been found that eye movements and the vestibulo-ocular reflex could potentially hinder one's ability to read and write effectively.⁶⁵ The vestibular system enables the enhancement of subsequent visual judgments using multisensory modulation, which involves the convergence of multiple sensory inputs.⁶⁶ The vestibular system activation might improve the consciousness and attention of the children, and it would be helpful for children suffering from dyslexia.⁶⁷

In their study, Marchesin *et al.* identified irregularities in the ability to voluntarily control saccadic eye movements across various conditions, including dyslexia, learning disorders, and ADHD.⁶⁸ Vestibular stimulation positively affects serotonin levels in the brain, promoting the growth of dendrites and synapses in hippocampal pyramidal neurons. It also inhibits the HPA and SAM axis, reducing stress levels that enhance learning and memory.⁶⁴

Individuals suffering from unilateral or bilateral vestibular loss commonly exhibit a deficit in visuospatial working memory. This deficit is evident across all age demographics and demonstrates a propensity for exacerbation with advancing age. This deterioration is attributed to the diminished functional capacity of the vestibular system, contributing to a progressive decline in cognitive function.⁶⁹

A recent study has discovered that brief vestibular and cognitive training enhances the reading speed of children with dyslexia and that improvement persists after one month. This study demonstrates the significant involvement of the vestibular system in developmental dyslexia. It highlights that dyslexia is influenced by deficiencies in gaze stabilization, impaired visual attention, and deficits in working memory. This study did not differentiate between vestibular and cognitive training, which are commonly responsible for improvement.¹⁶

Conclusion

Visuospatial memory, which involves the ability to remember and process visual information about objects and their spatial relationships, is crucial for improving reading and writing, as suggested by various sources in the literature. The vestibular system regulates this type

of memory, an intricate network of structures in the inner ear that contributes to our sense of balance and spatial orientation. Individuals with dysfunction or impairment in the vestibular system may encounter challenges related to developmental dyslexia and other neurodevelopmental disorders, which can affect their ability to read, write, and comprehend information. According to the findings of this review, it is suggested that the vestibular system may significantly impact developmental dyslexia. Furthermore, therapy based on the vestibular system has the potential to aid children suffering from this condition

References

- [1] Snowling MJ, Hulme C, Nation K. Defining and understanding dyslexia: past, present and future. *Oxford Rev Educ.* 2020; 46(4): 501. Available from: pmc/articles/PMC7455053/
- [2] Kirby P. Dyslexia debated, then and now: a historical perspective on the dyslexia debate. *Oxford Rev Educ.* 2020; 46(4): 472-86. doi.org/10.1080/03054985.2020.1747418
- [3] Elliott JG. It's time to be scientific about dyslexia. *Read Res Q.* 2020; 55(S1): S61-75.
- [4] Catts HW, Petscher Y. A cumulative risk and resilience model of dyslexia. *J Learn Disabil.* 2022; 55(3): 171-84. doi.org/10.1177/00222194211037062
- [5] The International Dyslexia Organisation. *IDA Dyslexia Handbook: What Every Family Should Know.* 2019; 21.
- [6] Wagner RK, Zirps FA, Edwards AA, Wood SG, Joyner RE, Becker BJ, et al. The prevalence of dyslexia: A New Approach to Its Estimation. 2020; 53(5): 354-65. doi.org/10.1177/0022219420920377
- [7] Yang L, Li C, Li X, Zhai M, An Q, Zhang Y, et al. Prevalence of Developmental Dyslexia in Primary School Children: A Systematic Review and Meta-Analysis. *Brain Sci.* 2022; 12(2): 240. pmc/articles/PMC8870220/
- [8] Arnett AB, Pennington BF, Peterson RL, Willcutt EG, DeFries JC, and Olson RK. Explaining the Sex Difference in Dyslexia. *Child Psychol Psychiatry.* 2017; 58(6): 719-727. doi: 10.1111/jcpp.12691
- [9] Snowling M, Hulme C. Do we really need a new definition of dyslexia? A commentary. *Ann Dyslexia.* 2024; 74(8): 0123456789. doi.org/10.1007/s11881-024-00305-y
- [10] Kim SK. Recent update on reading disability (Dyslexia) focused on neurobiology. *Clin Exp Pediatr.* 2021; 64(10): 497-503. doi.org/10.3345/cep.2020.01543
- [11] Roitsch J, Watson S. An overview of dyslexia: definition, characteristics, assessment, identification, and intervention. *Sci J Educ.* 2019; 7(4): 81-6. doi: 10.11648/j.sjedu.20190704.11
- [12] Stein J. What is developmental dyslexia? *Brain Sci.* 2018; 8: 26; doi:10.3390/brainsci8020026.
- [13] Stoodley CJ, Stein JF. Cerebellar function in developmental dyslexia. *Cerebellum.* 2013; 12(2): 267-76. doi: 10.1007/s12311-012-0407-1. PMID: 22851215.
- [14] Alvarez TA, Fiez JA. Current perspectives on the cerebellum and reading development. *Neurosci Biobehav Rev.* 2018; 92 : 55-66. doi.org/10.1016/j.neubiorev.2018.05.006
- [15] Ashburn SM, Flowers DL, Napoliello EM, Eden GF. Cerebellar function in children with and without dyslexia during single word processing. *Hum Brain Mapp.* 2020; 41(1): 120. doi: 10.1002/hbm.24792.
- [16] Caldani S, Moiroud L, Miquel C, Peiffer V, Florian A, Bucci MP. Short vestibular and cognitive training improves oral reading fluency in children with dyslexia. *Brain Sci.* 2021; 11: 1440. doi.org/10.3390/brainsci11111440.
- [17] Franceschini S, Bertoni S, Puccio G, Gori S, Termine C, Facoetti A. Visuo-spatial attention deficit in children with reading difficulties. *Sci Rep.* 2022; 12: 13930. doi.org/10.1038/s41598-022-16646-w
- [18] Bosse ML, Tainturier MJ, Valdois S. Developmental dyslexia: The visual attention span deficit hypothesis. *Cognition.* 2007; 104(2): 198-230. doi:10.1016/j.cognition.2006.05.009.
- [19] Paz Z. The History of Dyslexia. LDRFA. 2022. Available from: www.ldrfa.org/the-history-of-dyslexia/
- [20] Orton ST. Specific reading disability-strephosymbolia. *J Am Med Assoc.* 1928; 90: 1095-9. doi.org/10.1001/jama.1928.02690410007003
- [21] Paulesu E, Démonet JF, Fazio F, Crory EM, Chanoine V, Brunswick N, et al. Cultural diversity and biological unity in dyslexia. *Neuroimage.* 2001; 13(6): 584. doi:10.1016/s1053-8119(01)91927-5
- [22] Lyon GR. Toward a definition of dyslexia. *Ann Dyslexia.* 1995; 45: 1-27. doi: 10.1007/BF02648210
- [23] Lyon GR, Shaywitz SE, Shaywitz BA. A definition of dyslexia. *Ann Dyslexia.* 2003; 53: 1-14. doi: 10.1007/s11881-003-0001-9
- [24] Peterson RL, Pennington BF. Developmental dyslexia. *Annu Rev Clin Psychol.* 2015; 11: 283-307. doi:10.1146/annurev-clinpsy-032814-112842.
- [25] Eckert M. Neuroanatomical markers for dyslexia: A review of dyslexia structural imaging studies. *Neuroscientist.* 2004; 10(4): 362-71. doi:10.1177/1073858404263596
- [26] Kuhl U, Neef NE, Kraft I, Schaadt G, Dörr L, Brauer J, et al. The emergence of dyslexia in the developing brain. *NeuroImage.* 2020; 211: 116633. doi.org/10.1016/j.neuroimage.2020.116633
- [27] Benfatto MN, Seimyr GÖ, Ygge J, Pansell T, Rydberg A, Jacobson C. Screening for dyslexia using eye tracking during reading. *PLoS One.* 2016; 11(12): 1-16. doi:10.1371/journal.pone.0165508
- [28] Nerušil B, Polec J, Škunda J, Kačur J. Eye tracking based dyslexia detection using a holistic approach. *Sci Rep.* 2021; 11(1): 1-10. doi.org/10.1038/s41598-021-95275-1.
- [29] Lee MM, Stoodley C. Neural bases of reading fluency: A systematic review and meta-analysis. *bioRxiv.* 2023; 202: 885-1775. doi.org/10.1101/2023.09.25.559403
- [30] Spivey M, Spivey M, Spivey MJ, Armstrong BC, Spivey MJ, Fowler CA, et al. *The Cambridge Handbook of Psycholinguistics.* Cambridge University Press eBooks.

2012. doi.org/10.1017/cbo9781139029377
- [31] Wagley N, Booth JR. Neural pathways of phonological and semantic processing and its relations to children's reading skills. *Front Neurosci.* 2022; 16: doi.org/10.3389/fnins.2022.984328
- [32] Benischek A, Long X, Rohr CS, Bray S, Dewey D, Lebel C. Pre-reading language abilities and the brain's functional reading network in young children. *NeuroImage.* 2020; 217: 116903. doi.org/10.1016/j.neuroimage.2020.116903
- [33] Mechelh A, Humphreys GW, Mayall K, Olson A, Price CJ. Differential effects of word length and visual contrast in the fusiform and lingual gyri during reading. *Proc R Soc B Biol Sci.* 2000; 267(1455): 1909-13. doi 10.1098/rspb.2000.1229
- [34] Xia Z, Zhang L, Hoeft F, Gu B, Gong G, Shu H. Neural correlates of oral word reading, silent reading comprehension, and cognitive subcomponents. *Int J Behav Dev.* 2017; 42(3): 342-56. doi.org/10.1177/0165025417727872
- [35] Castles A, Rastle K, Nation K. Ending the reading wars: Reading acquisition from novice to expert. *PSPI.* 2018;19: 93. Available from: www.neuroscience.ox.ac.uk/publications/955461
- [36] Kearns DM, Hancock R, Hoeft F, Pugh KR, Frost SJ. The Neurobiology of dyslexia. *Teach Except Child.* 2019; 51(3): 175-88. doi.org/10.1177/0040059918820051
- [37] Stein J. Theories about developmental dyslexia. *Brain Sci.* 2023; 13(2): 208. doi.org/ 10.3390/brainsci13020208
- [38] Kuerten AB, Mota MB, Segart K. Developmental dyslexia: A condensed review of literature. *Ilha do Desterro.* 2019; 72(3): 249-70. doi.org/10.5007/2175-8026.2019v72n3p249
- [39] Ramus F. Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. *Brain.* 2003; 126(4): 841-65. doi.org/10.1093/brain/awg076
- [40] O'Brien G, Yeatman JD. Bridging sensory and language theories of dyslexia: Toward a multifactorial model. *Dev Sci.* 2021; 24(3): e13039. doi.org/10.1111/desc.13039
- [41] Denckla M, and Rudel R. Rapid "automatized" naming of pictured objects, colors, letters and numbers by normal children. *Cortex.* 1974; 10(2): 186-202. doi.org/10.1016/S0010-9452(74)80009-2
- [42] Wolf M, Bowers PG. Naming-speed processes and developmental reading disabilities. *J Learn Disabil.* 2000; 33(4): 322-4. doi.org/10.1177/002221940003300404
- [43] Wolf M, Bowers PG, Biddle K. Naming-speed processes, timing, and reading: a conceptual review. *J Learn Disabil.* 2000; 33(4): 387-407. doi: 10.1177/002221940003300409. PMID: 15493099.
- [44] Griffiths PG, Taylor RH, Henderson LM, Barrett BT. The effect of coloured overlays and lenses on reading: a systematic review of the literature. *Ophthalmic Physiol Opt.* 2016; 36(5): 519-44. doi: 10.1111/opo.12316
- [45] N. Sasikumar, M. Panimalar Roja and M. Parimala Fathima. Visuospatial skills and teaching learning process. *ISRJ.* 2014; 4(4): 493
- [46] Grabe W. Reading in a Second Language. *The Oxford Handbook of Applied Linguistics*, (2 Ed). 2012.
- [47] Baddeley A. Working memory. *Comptes Rendus de L'Académie des Sciences - Series III - Sciences de la Vie*, 1998; 321(2-3): 167-73. doi.org/10.1016/S0764-4469(97)89817-4
- [48] Pham AV, & Hasson RM. Verbal and visuospatial working memory as predictors of children's reading ability. *Arch Clin Neuropsychol.* 2014; 29(5): 467-77. https://doi.org/10.1093/arclin/acu024
- [49] Bazan B. Visuospatial working memory and the hybrid reading fluency measure. *RFL.* 2021; 33(2): 141-67. Available from: http://hdl.handle.net/10125/67398.
- [50] Liu S, Wei W, Chen Y, Hugo P and Zhao J. Visual-spatial ability predicts academic achievement through arithmetic and reading abilities. *Front Psychol.* 2021; 11: 591308. doi: 10.3389/fpsyg.2020.591308
- [51] Franceschini S, Bertoni S, Puccio G, Gori S, Termine C, and Facoetti A. Visuo-spatial attention deficit in children with reading difficulties. *Sci Rep.* 2022; 12(1): 1-10. doi.org/10.1038/s41598-022-16646-w
- [52] Taran N, Farah R, DiFrancesco M, Altaye M, Vannest J, Holland S, Rosch K, Schlaggar BL, Horowitz-Kraus T. The role of visual attention in dyslexia: Behavioral and neurobiological evidence. *Hum Brain Mapp.* 2022; 43(5): 1720-37. doi: 10.1002/hbm.25753. Epub 2022 Jan 3.
- [53] Peterson RL, Pennington BF. Developmental dyslexia. *Lancet.* 2012; 379(9830): 1997-2007. doi: 10.1016/S0140-6736(12)60198-6. Epub 2012 Apr 17.
- [54] Giovagnoli G, Vicari S, Tomasetti S, Menghini D. The role of visual-spatial abilities in dyslexia: Age differences in children's reading? *Front Psychol.* 2016; 7: 1997. doi: 10.3389/fpsyg.2016.01997.
- [55] Nevo E, and Bar-Kochva I. The relations between early working memory abilities and later developing reading skills: A longitudinal study from kindergarten to fifth grade. *Mind Brain Educ.* 2015; 9(3): 154-63. doi.org/10.1111/mbe.12084
- [56] Peng P, Barnes M, Wang C, Wang W, Li S, Swanson HL, Dardick W, Tao S. A meta-analysis on the relation between reading and working memory. *Psychol Bull.* 2018; 144(1): 48-76. doi: 10.1037/bul0000124. Epub 2017 Oct 30.
- [57] Gray S, Fox AB, Green S, Alt M, Hogan TP, Petscher Y, Cowan N. Working Memory Profiles of Children With Dyslexia, Developmental Language Disorder, or Both. *J Speech Lang Hear Res.* 2019; 62(6): 1839-58. doi: 10.1044/2019_JSLHR-L-18-0148. Epub 2019 May 20.
- [58] von Károlyi C, Winner E, Gray W, Sherman GF. Dyslexia linked to talent: global visual-spatial ability. *Brain Lang.* 2003; 85(3): 427-31. doi: 10.1016/s0093-934x(03)00052-x.
- [59] Jamon M. The development of vestibular system and related functions in mammals: impact of gravity. *Front Integr Neurosci.* 2014; 8: 11. doi: 10.3389/fnint.2014.00011.

- [60] Cullen K, Sadeghi S. Vestibular system. Scholarpedia. 2008; 3(1): 3013. <http://dx.doi.org/10.4249/scholarpedia.3013>.
- [61] Levinson HN. The cerebellar-vestibular basis of learning disabilities in children, adolescents and adults: hypothesis and study. *Percept Mot Skills*. 1988; 67(3): 983-1006. doi: 10.2466/pms.1988.67.3.983. Erratum in: *Percept Mot Skills* 1989 Feb;68(1)
- [62] Franco ES, Panhoca I. Vestibular function in children underperforming at school. *Braz J Otorhinolaryngol*. 2008; 74(6): 815-25. doi: 10.1016/S1808-8694(15)30141-5. PMID: 19582337; PMCID: PMC9445963.
- [63] Bigelow RT, Agrawal Y. Vestibular involvement in cognition: Visuospatial ability, attention, executive function, and memory. *J Vestib Res*. 2015; 25(2): 73-89. doi: 10.3233/VES-150544.
- [64] Sailesh KS, Manyam R, Jinu KV, et al. Beneficial effects of vestibular stimulation on learning and memory: an overview. *MOJ Anat & Physiol*. 2018; 5(3): 212–213. doi: 10.15406/mojap.2018.05.00194.
- [65] Sales R, Colafêmina JF. The Influence of eye movement and the vestibularocular reflex in reading and writing. A influência da oculomotricidade e do reflexo-vestibulo-ocular na leitura e escrita. 2014; (6): 1791-7. doi.org/10.1590/1982-0216201419013
- [66] Smith L, Gkioka A, Wilkinson D. Vestibular-guided visual search. *Exp Brain Res*. 2020; 238(3): 689-98. doi.org/10.1007/s00221-020-05741-x
- [67] Haghighoo H. Vestibular therapy improved motor planning, attention, and balance in children with attention deficit hyperactivity disorders: a randomized controlled trial. *Phys Med Rehabil Res*. 2018; 3(2): 1-6. doi: 10.15761/PMRR.1000171
- [68] Marchesin VC, Caovilla HH, Ganança MM. Dos movimentos oculares sacádicos em crianças com desordens do processamento auditivo. *Acta ORL*. 2005; 23(2): 7-12.
- [69] Guidetti G, Guidetti R, Manfredi M, Manfredi M. Vestibular pathology and spatial working memory. *Acta Otorhinolaryngol Ital*. 2020; 40(1): 72-8. doi: 10.14639/0392-100X-2189. Epub 2019 Jul 31.

COVID-19 vaccination doesn't influence sperm motility, concentration, and morphology

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ABSTRACT

Background: The COVID-19 pandemic, driven by SARS-CoV-2, necessitated the rapid development and global deployment of vaccines. Despite the high efficacy of vaccines like AstraZeneca and Pfizer-BioNTech in preventing severe COVID-19, concerns about potential side effects, particularly on male fertility, have arisen.

Objective: This study aims to evaluate the impact of COVID-19 vaccination on key sperm parameters (motility, concentration, count, and morphology) and serum interleukin-6 (IL-6) levels in men.

Materials and methods: A cross-sectional study was conducted over six months (March to August 2022) at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in Baghdad, Iraq. The study included 63 participants divided into three groups: AstraZeneca vaccine group (N=24), Pfizer vaccine group (N=19), and an unvaccinated control group (N=20). Participants' sperm parameters were analyzed following the WHO guidelines, and serum IL-6 levels were measured using ELISA.

Results: No statistically significant differences were found in sperm motility, concentration, total sperm count, or morphology between vaccinated and unvaccinated groups. Specifically, sperm motility was $57.3 \pm 8.9\%$ in the vaccinated group versus $56.8 \pm 9.2\%$ in the control group ($p=0.782$). Sperm concentration was 62.5 ± 14.7 M/mL in the vaccinated group compared to 61.9 ± 15.1 M/mL in the control group ($p=0.845$). Total sperm count was 185.6 ± 43.8 M in the vaccinated group versus 183.2 ± 44.5 M in the control group ($p=0.802$). Morphologically normal sperm were $4.2 \pm 1.1\%$ in the vaccinated group versus $4.1 \pm 1.0\%$ in the control group ($p=0.659$). Serum IL-6 levels showed no significant differences between the groups.

Conclusion: COVID-19 vaccination with either AstraZeneca or Pfizer-BioNTech does not adversely affect sperm parameters or induce significant changes in serum IL-6 levels. These findings support the safety of COVID-19 vaccines concerning male reproductive health, alleviating concerns about potential adverse effects on fertility.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented unprecedented challenges to global public health.¹⁻³ In response to this crisis, the rapid development and deployment of vaccines have been necessary to mitigate the disease's spread and severity.⁴ Among the various vaccines developed, the AstraZeneca and Pfizer-BioNTech vaccines have been widely administered worldwide, demonstrating high efficacy in preventing severe COVID-19 outcomes.^{5,6} Despite the proven benefits of vaccination, concerns about potential side effects have emerged, including speculations about

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impacts on fertility.⁷ These concerns have been particularly pronounced among men of reproductive age, potentially influencing vaccine hesitancy in this demographic.⁸ The male reproductive system, specifically the testes, has been identified as a probable target for SARS-CoV-2 due to the expression of angiotensin-converting enzyme 2 (ACE2) receptors in testicular cells.⁹ This raised questions about whether the immune response triggered by COVID-19 vaccines might similarly affect testicular function and sperm quality.

Sperm parameters, including motility, concentration, count, and morphology, are critical indicators of male fertility potential.^{10,11} Any significant alterations in these parameters could have implications for reproductive health. Moreover, systemic inflammation, assessed through biomarkers such as interleukin-6 (IL-6), has been associated with impaired spermatogenesis and reduced sperm quality.¹² Given that vaccines stimulate an immune response, it is essential to investigate whether this response affects sperm parameters or induces systemic inflammation that could impact male fertility.

Previous studies have explored the effects of COVID-19 infection on male reproductive function, with some suggesting potential negative impacts.^{13,14} However, research on the specific effects of COVID-19 vaccination on sperm parameters and relevant inflammatory markers remains unclear. Therefore, and in light of these considerations, this study aims to evaluate the potential effects of COVID-19 vaccination, specifically the AstraZeneca and Pfizer-BioNTech vaccines, on key sperm parameters (motility, concentration, count, and morphology) and serum IL-6 levels.

Materials and methods

Study design subjects

This cross-sectional study was conducted from March to August 2022 at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies (Baghdad, Iraq). A total of 63 participants were included, divided into three groups: the AstraZeneca vaccine group (N=24), the Pfizer vaccine group (N=19), and the unvaccinated control group (N=20). Participants were assigned to groups based on their vaccination status, with the control group matched to the vaccinated groups for age.

Inclusion criteria for the study were: male participants aged 18-45 years; for the vaccinated groups, participants who received exactly two doses of either vaccine type, with the second dose administered 3-6 months before sample collection; for the control group, individuals who had not received any COVID-19 vaccine; no history of COVID-19 infection; and no known fertility issues. The exclusion criteria included: history of testicular surgery or trauma; current use of medications known to affect spermatogenesis; chronic medical conditions that could influence fertility (e.g., diabetes, thyroid disorders); Body Mass Index (BMI) >35 kg/m²; excessive alcohol consumption (>14 units per week); current smokers; use of recreational drugs; and fever (>38 °C) within the three months preceding sample collection.

The study received approval from the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University's Ethics Committee (No.0702-PF-2024R34, on March 10th, 2022).

Demographic data collection

Demographic information and medical history were collected from all participants through a standardized questionnaire. The questionnaire included age, height, weight, occupation, lifestyle factors (such as exercise habits and diet), and detailed vaccination history for the vaccinated groups. For the vaccinated participants, information on the type of vaccine received (AstraZeneca or Pfizer), number of doses, and vaccination dates were recorded. All participants were also asked about any history of COVID-19 infection, other recent illnesses, and medication use. The questionnaires were administered by trained research staff, and all data were entered into a secure, password-protected database to ensure confidentiality.

Semen sample collection

Semen samples were collected from all participants following a period of 2-7 days of sexual abstinence. Participants were provided with clear, written instructions on proper sample collection. Samples were obtained through masturbation and collected in sterile, wide-mouthed containers. The containers were labeled with a unique identifier code to maintain participant anonymity. Immediately after collection, the samples were placed in an incubator at 37 °C and processed within one hour of collection to ensure sample integrity.

Semen analysis

Semen analysis was performed according to the World Health Organization (WHO) laboratory manual for examining and processing human semen (5th Ed, 2010). Two laboratory technicians performed all semen analyses, with cross-validation of 20% of samples. The study included an assessment of sperm motility, concentration, total sperm count, and morphology. Sperm motility was evaluated using a computer-aided sperm analysis (CASA) system. Sperm concentration was determined using a Makler counting chamber. Total sperm count was calculated by multiplying the concentration by the semen volume. Sperm morphology was assessed using Diff-Quik stained smears, with at least 200 spermatozoa evaluated per sample. All analyses were performed by trained laboratory technicians blinded to the participants' vaccination status to prevent bias.

IL-6 measurement

Blood samples were collected from all participants on the same day as semen sample collection. Venous blood (5 mL) was drawn from the antecubital vein into serum separator tubes. The blood was allowed to clot at room temperature for 30 minutes, then centrifuged at 1500 x g for 15 minutes to separate the serum. According to the manufacturer's instructions, Serum IL-6 levels were

measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, USA). All samples were run in duplicate, and the average of the two measurements was used for analysis. The assay's sensitivity was 0.7 pg/mL, with an intra-assay coefficient of variation of <10%.

Statistical analysis

Statistical analyses were performed using RStudio with R version 4.2.1. Descriptive statistics were calculated for all variables. The Shapiro-Wilk test was used to assess the normality of data distribution. For comparing sperm

parameters and IL-6 levels across the three groups (AstraZeneca, Pfizer, and Control), one-way ANOVA was employed, followed by Tukey's post-hoc test for pairwise comparisons if ANOVA showed significant differences. A $p < 0.05$ was considered statistically significant.

Results

Table 1 presents the anthropometric characteristics of the study participants. Analysis of these data revealed no statistically significant differences in age, height, weight, or BMI among the AstraZeneca, Pfizer, and Control groups ($p > 0.05$).

Table 1. Anthropometric characteristics of study participants by vaccination group.

Characteristic	AstraZeneca (N=24)	Pfizer (N=19)	Control (N=20)	p value
Age (years)	34.6±5.2	35.2±4.8	33.9±5.5	0.723
BMI (kg/m ²)	26.0±3.1	26.3±3.3	25.4±2.9	0.621

Note: Values are presented as mean±SD, BMI: body mass index. All p values were calculated using one-way ANOVA.

To assess the potential impact of COVID-19 vaccination on sperm parameters, the vaccinated groups (AstraZeneca and Pfizer combined) were compared with the non-vaccinated control group (Figure 1). The analysis of sperm motility showed no significant difference between the vaccinated ($57.3 \pm 8.9\%$) and non-vaccinated ($56.8 \pm 9.2\%$) groups ($p = 0.782$). The sperm concentration was also comparable between the vaccinated (62.5 ± 14.7 M/mL) and non-vaccinated (61.9 ± 15.1 M/mL) groups ($p = 0.845$). The total sperm count also showed no significant difference,

with the vaccinated group averaging 185.6 ± 43.8 M and the non-vaccinated group 183.2 ± 44.5 M ($p = 0.802$). Further analysis of sperm morphology revealed that the percentage of morphologically normal sperm was similar between the vaccinated ($4.2 \pm 1.1\%$) and non-vaccinated ($4.1 \pm 1.0\%$) groups ($p = 0.659$). These results together suggest that COVID-19 vaccination does not significantly affect the main parameters of sperm quality in this study population.

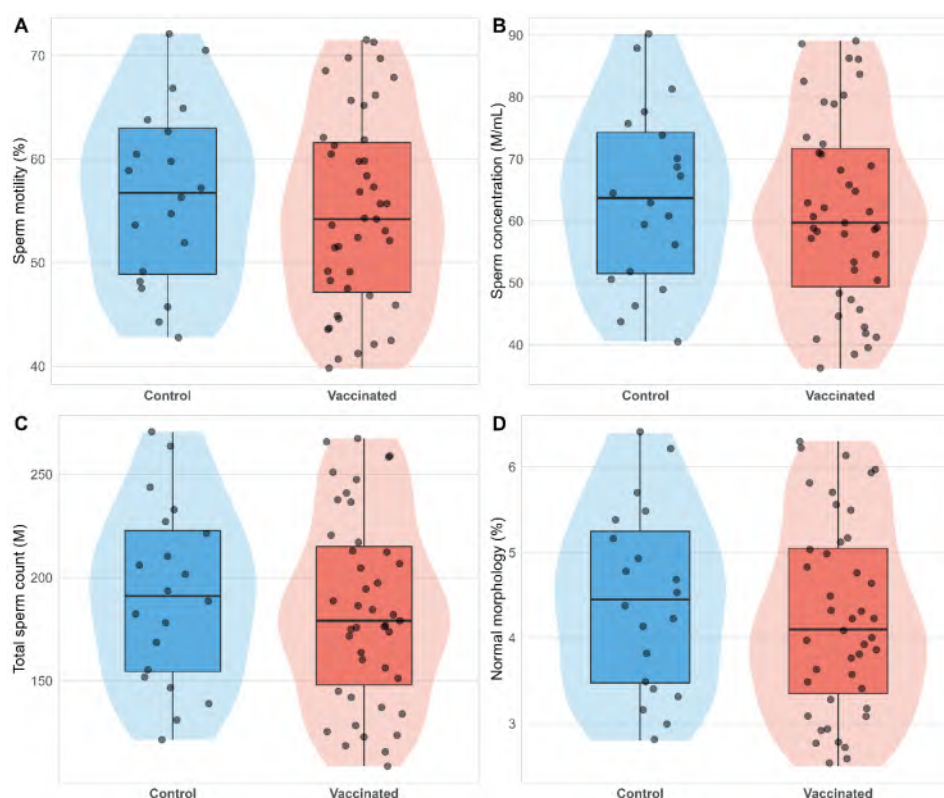


Figure 1. Sperm parameters of vaccinated (AstraZeneca or Pfizer, N=43) and unvaccinated control (N=20) groups. A: sperm motility (%), B: sperm concentration (M/mL), C: total sperm count (M), D: normal morphology (%). Box plots show the median, quartiles (box), and range (whiskers); dots represent individual values. The vaccinated group includes AstraZeneca (N=24) and Pfizer (N=19) recipients. No significant differences were found between groups ($p > 0.05$).

The effects of COVID-19 vaccination on sperm parameters were evaluated by comparing AstraZeneca-vaccinated, Pfizer-vaccinated, and unvaccinated control (N=20) groups. Figure 2 presents the results of motility, concentration, total count, and normal morphology. The analysis revealed non-statistically significant differences among the three groups for the measured parameters. The sperm motility was comparable across AstraZeneca ($55.2 \pm 10.1\%$), Pfizer ($54.3 \pm 9.2\%$), and control ($56.1 \pm 9.8\%$) groups ($p=0.808$). Similarly, sperm concentration showed no significant differences, with AstraZeneca, Pfizer, and control groups averaging 60.3 ± 14.8 M/mL, 62.1 ± 13.9 M/mL, and 59.2 ± 15.2 M/mL, respectively ($p=0.380$). Total sperm count also remained consistent across groups, with mean values of 180.5 ± 44.7 M, 185.2 ± 39.8 M, and 178.3 ± 49.4 M for AstraZeneca, Pfizer, and control groups, respectively ($p=0.859$). Lastly, the percentage of sperm with normal morphology was similar among AstraZeneca ($4.0 \pm 1.0\%$), Pfizer ($4.1 \pm 0.9\%$), and control ($4.2 \pm 1.0\%$) groups ($p=0.790$). To further investigate the distribution of sperm parameters across vaccination groups, density

analysis was performed (Figure 3). The study of sperm motility revealed relatively similar distributions across all three groups, with most values falling between 45% and 70%. The AstraZeneca group showed a slightly wider distribution than the Pfizer and control groups, but this difference was not statistically significant (Kolmogorov-Smirnov test, $p=0.213$ and $p=0.189$, respectively). In addition, sperm concentration distributions were comparable among the three groups, with most values ranging from 40 to 80 M/mL. The Pfizer group exhibited a minor skew towards higher concentrations, but this trend did not reach statistical significance ($p=0.167$ compared to AstraZeneca, $p=0.144$ compared to control). Total sperm count distributions mirrored the concentration patterns, with no significant differences observed among the groups ($p>0.05$ for all). Lastly, among the sperm parameters, the distribution of normal sperm morphology was notably consistent across all groups, with most values falling between 2% and 6%. No significant differences were detected in the shape or spread of these distributions ($p>0.05$).

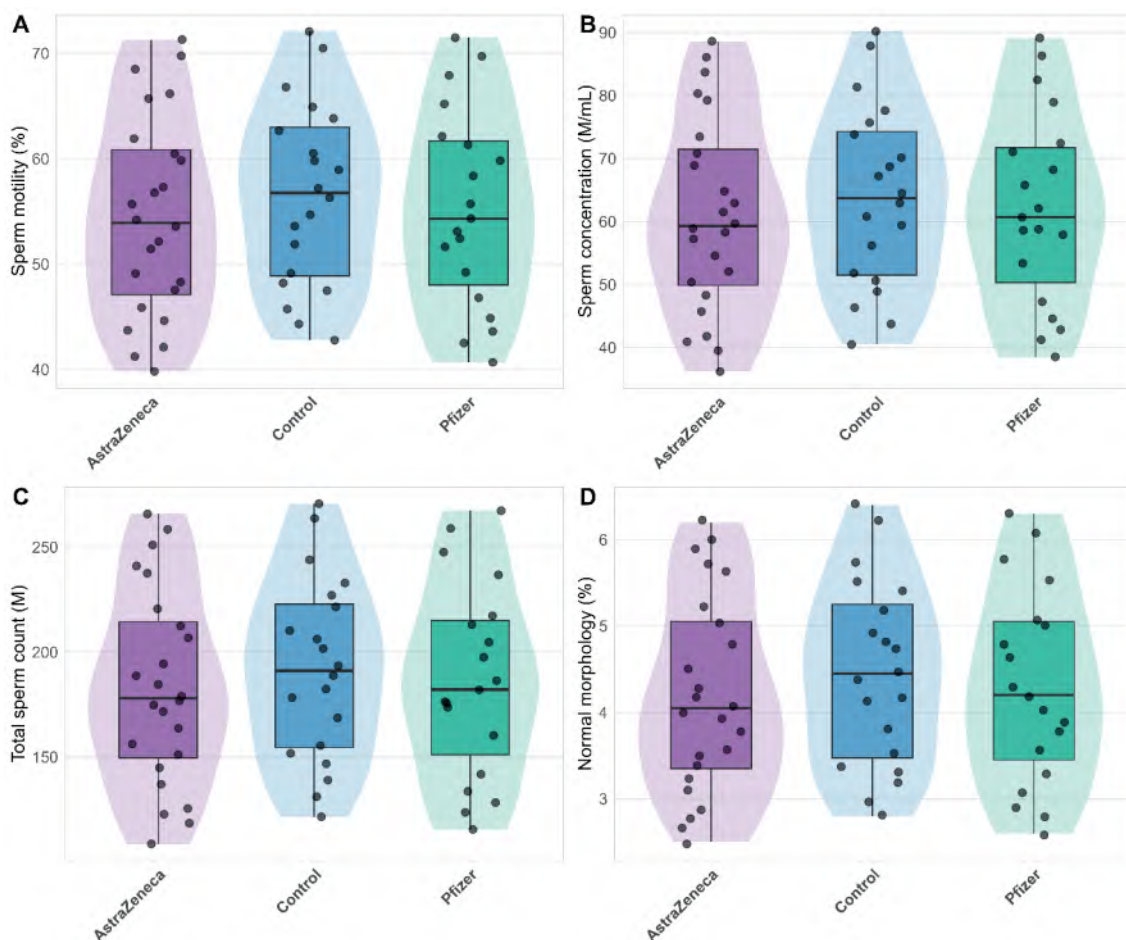


Figure 2. Sperm parameters of AstraZeneca (N=24), Pfizer (N=19), and control (N=20) groups. A: sperm motility (%), B: sperm concentration (M/mL), C: total sperm count (M), D: normal morphology (%). Box plots show the median, quartiles (box), and range (whiskers); dots represent individual values. No significant differences were found among groups ($p>0.05$).

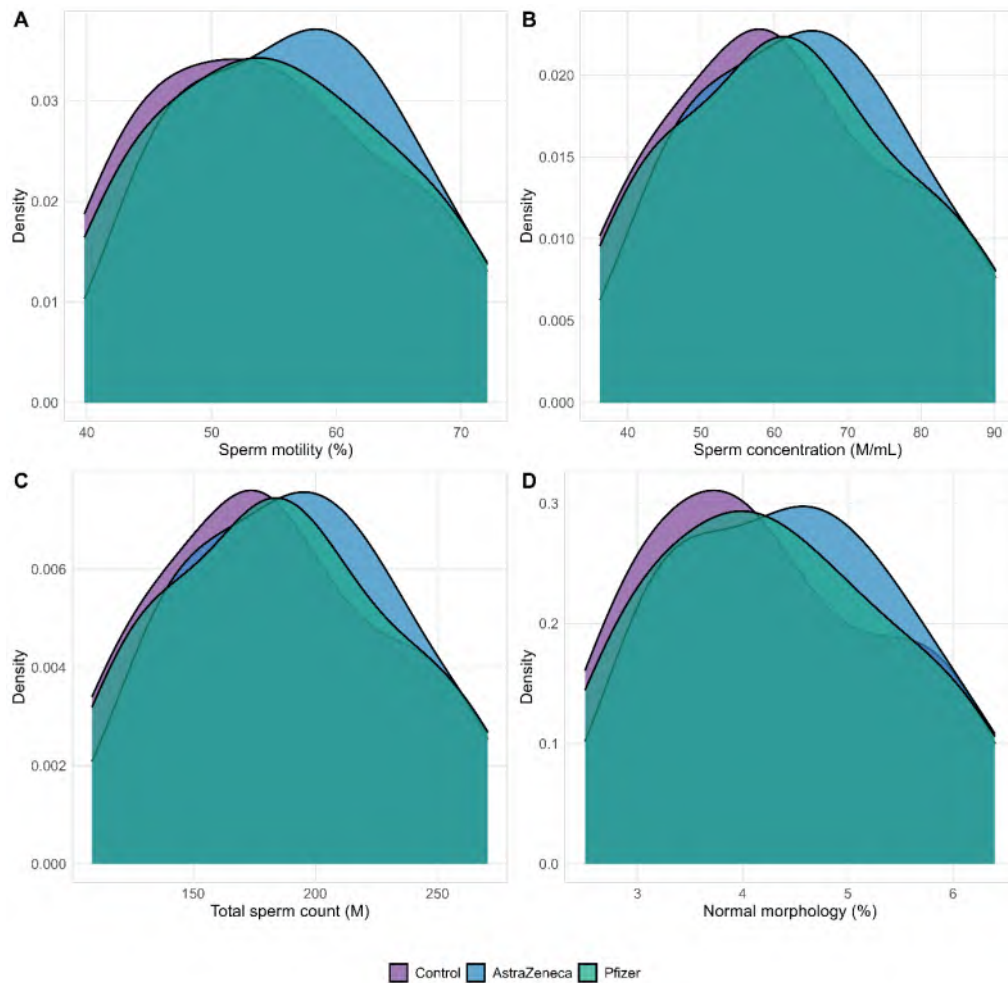


Figure 3. Distribution of sperm parameters in AstraZeneca, Pfizer, and control groups. A: sperm motility (%), B: sperm concentration (M/mL), C: total sperm count (M), D: normal morphology (%). Density plots show the distribution pattern for each group. No significant differences were found between distributions ($p>0.05$).

The levels of IL-6 were also assessed for the same groups (Figure 4). The results showed non-significant differences between the vaccinated and non-vaccinated groups ($p>0.05$, Figure 4A), and the type of vaccine didn't change the results (Figure 4B). However, it showed

slightly more variability in distribution, with the control group displaying a marginally more comprehensive range (Figure 4C). However, statistical analysis confirmed these differences were insignificant ($p=0.231$ for AstraZeneca vs. control, $p=0.256$ for Pfizer vs. control).

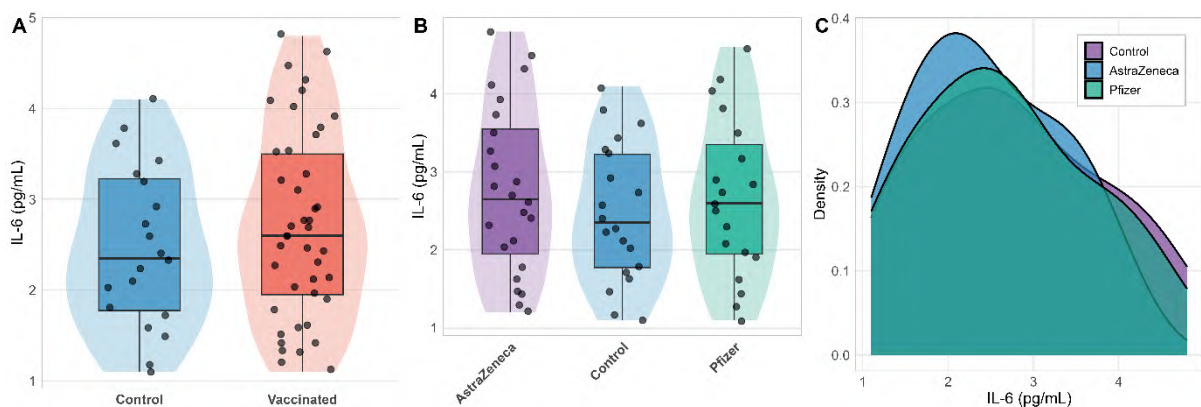


Figure 4. IL-6 levels across groups. A: comparison between vaccinated and control groups, B: comparison among AstraZeneca, Pfizer, and control groups, C: distribution pattern for each group. Box plots show the median, quartiles (box), and range (whiskers); dots represent individual values. No significant differences were found between groups ($p>0.05$).

Discussion

This study investigated the potential effects of COVID-19 vaccination on key sperm parameters and serum IL-6 levels in men of reproductive age. These findings demonstrate that immunization with the AstraZeneca or Pfizer-BioNTech COVID-19 vaccines does not significantly impact sperm motility, concentration, count, or morphology compared to unvaccinated controls. Additionally, no significant differences in serum IL-6 levels between vaccinated and unvaccinated individuals were observed.

The lack of significant differences in sperm parameters between vaccinated and unvaccinated groups aligns with recent studies examining the impact of COVID-19 vaccines on male fertility. Gonzalez *et al.* (2021) found no significant decreases in sperm parameters among 45 men after receiving two mRNA COVID-19 vaccines.¹⁵ Relatedly, Barda, *et al.* reported no deleterious effects on sperm quality following BNT162b2 mRNA vaccination in a cohort of 37 sperm donors.¹⁶ The current study's results extend these findings by including both mRNA (Pfizer-BioNTech) and viral vector (AstraZeneca) vaccines and suggest that different vaccine platforms do not differentially affect sperm quality.

The stability of sperm parameters post-vaccination is particularly noteworthy given the concerns about the potential impacts of COVID-19 itself on male fertility. Studies have shown that SARS-CoV-2 infection can lead to impaired spermatogenesis and reduced sperm quality, possibly due to the expression of ACE2 receptors in testicular cells.^{17,18} The findings indicate that the immune response triggered by vaccination does not induce similar detrimental effects on spermatogenesis, which is reassuring for men considering vaccination.

The analysis of serum IL-6 levels provides further insight into the systemic effects of COVID-19 vaccination. IL-6 is a critical pro-inflammatory cytokine associated with impaired spermatogenesis when chronically elevated.^{12,19} The lack of significant differences in IL-6 levels between vaccinated and unvaccinated groups suggests that COVID-19 vaccination does not induce a persistent inflammatory state that could potentially impact sperm production. This is consistent with the transient nature of vaccine-induced immune responses and supports the overall safety profile of COVID-19 vaccines.

The study's strengths include comparing two different vaccine types, including a matched control group, and the comprehensive assessment of multiple sperm parameters. However, certain limitations should be acknowledged. First, the small sample size in each group may limit statistical power. Second, as a single-center study, the generalizability of results to broader populations may be limited. Third, the cross-sectional nature of the survey allows for assessment at only one time point, without the ability to track temporal changes or establish long-term effects. Fourth, patient self-reports obtained vaccination information, which may introduce reporting bias. To confirm these findings, future multi-center studies with larger sample sizes and longitudinal designs are needed.

Conclusion

The current study demonstrates that COVID-19 vaccination with either AstraZeneca or Pfizer-BioNTech vaccines does not adversely affect key sperm parameters or induce systemic inflammation as measured by serum IL-6 levels. These findings support the safety of COVID-19 vaccines concerning male reproductive function and can help inform decision-making for men considering vaccination. Future research on larger cohorts, longer-term follow-up, and the inclusion of other vaccine types to further analyze these observations is needed.

Conflict of interest

The author declares no competing interests.

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References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. 2020; 382(8): 727-33. doi: 10.1056/NEJMoa2001017
- [2] Luay A, Mohsen Al-Essawe E, Al-Kawaz U. Prevalence of erectile dysfunction in males post COVID-19 infection. Iraqi J Embryos Infertil Res. 2021; 11(1): 89-98. Available from: <https://ijeir.net/index.php/ijeir/article/view/70>
- [3] Chandramouli T, Mishra SB, Rath A. Reinfection of SARS CoV-2 in patients with relapse of symptoms after clinical recovery: A case series. J Assoc Med Sci. 2022; 55(3): 105-8. Available from: <https://he01.tci-thaijo.org/index.php/bulletinAMS/article/download/255037/174080>
- [4] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al.* Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020; 383(27): 2603-15. doi/10.1056/NEJMoa2034577
- [5] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021; 397(10269): 99-111. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673620326611>
- [6] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021; 384(5):403-16. doi/10.1056/NEJMoa2035389
- [7] Diaz P, Reddy P, Ramasahayam R, Kuchakulla M, Ramasamy R. COVID-19 vaccine hesitancy linked to

- increased internet search queries for side effects on fertility potential in the initial rollout phase following Emergency Use Authorization. *Andrologia*. 2021; 53(9):e14156. doi/10.1111/and.14156
- [8] Roozenbeek J, Schneider CR, Dryhurst S, Kerr J, Freeman ALJ, Recchia G, *et al.* Susceptibility to misinformation about COVID-19 around the world. *R Soc Open Sci*. 2020; 7(10): 201199. doi/10.1098/rsos.201199
- [9] Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, Leydig and Sertoli cells. *Cells*. 2020; 9(4): 920. Available from: <https://www.mdpi.com/2073-4409/9/4/920>
- [10] Guzik DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, *et al.* Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med*. 2001; 345(19): 1388-93. doi/abs/10.1056/NEJMoa003005
- [11] Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HWG, Behre HM, *et al.* World Health Organization reference values for human semen characteristics*. *Hum Reprod Update*. 2010; 16(3):231-45. Available from: <http://academic.oup.com/humupd/article/16/3/231/639175/World-Health-Organization-reference-values-for>
- [12] Moretti E, Cosci I, Spreafico A, Serchi T, Cuppone AM, Collodel G. Semen characteristics and inflammatory mediators in infertile men with different clinical diagnoses. *Int J Androl*. 2009; 32(6): 637-46. doi/10.1111/j.1365-2605.2008.00911.x
- [13] Erbay G, Sanli A, Turel H, Yavuz U, Erdogan A, Karabakan M, *et al.* Short-term effects of COVID-19 on semen parameters: A multicenter study of 69 cases. *Andrology*. 2021;9(4): 1060-5. doi/10.1111/andr.13019
- [14] Gacci M, Coppi M, Baldi E, Sebastianelli A, Zaccaro C, Morselli S, *et al.* Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19. *Hum Reprod*. 2021; 36(6):1520-9. Available from: <https://academic.oup.com/humrep/article/36/6/1520/6125160>
- [15] Gonzalez DC, Nassau DE, Khodamoradi K, Ibrahim E, Blachman-Braun R, Ory J, *et al.* Sperm parameters before and after COVID-19 mRNA vaccination. *JAMA*. 2021; 326(3): 273-4. doi: 10.1001/jama.2021.9976
- [16] Barda S, Laskov I, Grisaru D, Lehavi O, Kleiman S, Wenkert A, *et al.* The impact of COVID-19 vaccine on sperm quality. *Int J Gynecol Obstet*. 2022; 158(1): 116-20. doi/10.1002/ijgo.14135
- [17] Li H, Xiao X, Zhang J, Zafar MI, Wu C, Long Y, *et al.* Impaired spermatogenesis in COVID-19 patients. *EClinicalMedicine*. 2020; 28:100604. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2589537020303485>
- [18] Navarra A, Albani E, Castellano S, Arruzzolo L, Levi-Setti PE. Coronavirus disease-19 infection: Implications on male fertility and reproduction. *Front Physiol*. 2020; 11. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2020.574761/full>
- [19] Qian L, Sun G, Zhou B, Wang G, Song J, He H. Study on the relationship between different cytokines in the semen of infertility patients. *Am J Reprod Immunol*. 2011; 66(2): 157-61. doi/10.1111/j.1600-0897.2010.00980.x

Alternative X-ray attenuation material from iodide-starch-gel-based materials

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ABSTRACT

Background: Iodine is often used as a contrast media because the k-shell binding energy (K-edge) is 33.2 keV, the average energy of a diagnostic X-ray. Thus, iodine can be utilized as a radiation attenuation material for X-rays.

Objective: This study aimed to produce low-energy X-ray attenuation materials used as X-ray shielding. A sodium iodide compound will be synthesized by polymerizing mung bean starch with sodium iodide.

Materials and methods: The iodide-starch-gel-based material (ISG) was made by mixing a mung bean starch solution (10 %w/w) with a sodium iodide (NaI) solution (100, 200, 250, and 300 mg-Iodine/gm). The linear attenuation coefficient (μ) was determined using radiation dose acquired from the DR plate system and CdTe detector. The X-rays were done at 50 - 120 kVp to study the attenuation properties.

Results: The results showed that the linear attenuation coefficient of t ISG was slightly higher than that of sodium iodide solution at the same concentration. The spectrum still shows an X-ray absorption characteristic at about 30.1-40.5 keV K-edge range.

Conclusion: Iodide-starch-gel-based components can attenuate X-ray with a K-edge range from 30-40 kVp. The attenuation coefficient of X-ray radiation varies linearly with energy level. Moreover, the concentration of the NaI solution is directly proportional to the attenuation of X-ray radiation. Thus, based on these properties and the gel-like consistency of the substance, it can be developed into a surface coating material to reduce X-ray radiation exposure.

Introduction

X-radiation is routinely used in medical imaging to diagnose mild radiation effects; however, low-dose and low-energy X-rays may affect the cellular level change.¹⁻³ The k-shell binding energy of iodine and barium is similar to the average energy of a diagnostic X-ray. Therefore, those compounds are widely used as a contrast media in medical imaging and a non-particle ionizing radiation detector.^{4,5} However, the iodide-containing compound induced acute kidney injury (AKI), and DNA damage.^{5,6} The effects of iodine contrast agents on cellular functions of human peripheral blood mononuclear at a concentration of 50 mg-iodine/mL of iodine contrast media causes a 50% reduction in cell viability. Still, lower concentrations of 2.5, 5.0, and 10.0 mg-iodine/mL do not affect the cell cycle.⁷ Previous studies have found that new lead-free shielding materials have radiation-shielding properties by using components with high-atomic-number substances⁸ such as tungsten trioxide (WO_3), barium sulfate (BaSO_4), bismuth oxide (Bi_2O_3), and molybdenum trioxide (MoO_3).⁹

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Although iodide-containing compounds increase toxicity, they retain radiation attenuation properties because of the iodine in sodium iodide. So, it can be applied to utilize the radiation attenuation material.

This study aims to produce low-energy X-ray attenuation materials used as X-ray shielding by using a sodium iodide compound and the polymerization of mung bean starch.

Material and methods

Agent and Solution Preparation

Iodide-Starch-Gel Based Materials (ISG) is a mixture of mung bean starch (MBS) and sodium iodide (NaI) solution (100, 200, 250 and 300 mg-iodine/gm). First, prepare a solution of sodium iodide. Then, MBS powder was dissolved into the sodium iodide solution to get the final concentration of MBS solution at 10 %w/w. A standard sodium iodide (NaI) solution was prepared at various concentrations of 100, 200, and 300 mg-iodine/g. Mung bean starch (MBS 10%w/w) was dissolved with distillation water. The contrast agents as barium sulfate (BaSO_4) were dissolved with distillation water (H_2O) in a ratio of 1:1. And iodinated-base contrast omnipaque (OM) (Iohexol 300 mg-iodine/mL, GE Healthcare) and telebrix 35 (TE) (Ioxitalamate meglumine sodium 350 mg-iodine/mL, GUERBET France) were used. All materials were filled with 1, 2, and 3 cm thicknesses in plastic containers.

Measurements of the X-ray linear attenuation coefficient

The attenuated photons absorbed or scattered per unit thickness of the absorber are expressed as the linear attenuation coefficient (μ). The Beer-Lambert Rule describes the linear attenuation coefficient of X-ray as the following equation.

$$I = I_0 e^{-\mu X}$$

Where:

I: the intensity of photons transmitted across some distance X

I_0 : the initial intensity of photons

μ : the linear attenuation coefficient (cm^{-1})

X: distance traveled (cm)

The diagnostic X-ray machine (Shimadzu RADspeed Pro) with a filter of 0.5 mm aluminum was used to perform the initialized radiation. To determine the linear attenuation coefficient, all materials were exposed at a source-to-image distance (SID) of 180 cm at various energy settings at 50, 60, 70, 80, 90, and 100 kVp with 4 and 5 milliampere-seconds (mAs). A digital radiography plate (DR) of 14x17 square inches (FUJIFILM FDR D-EVO plus C35i) was applied to record the initial intensity (I_0) and the transmitted intensity (I) of radiation through all materials. To estimate the initial radiation intensity, an aluminum 11-step wedge with a step of 3 mm rise was exposed parallel with all materials. (Figure 1)

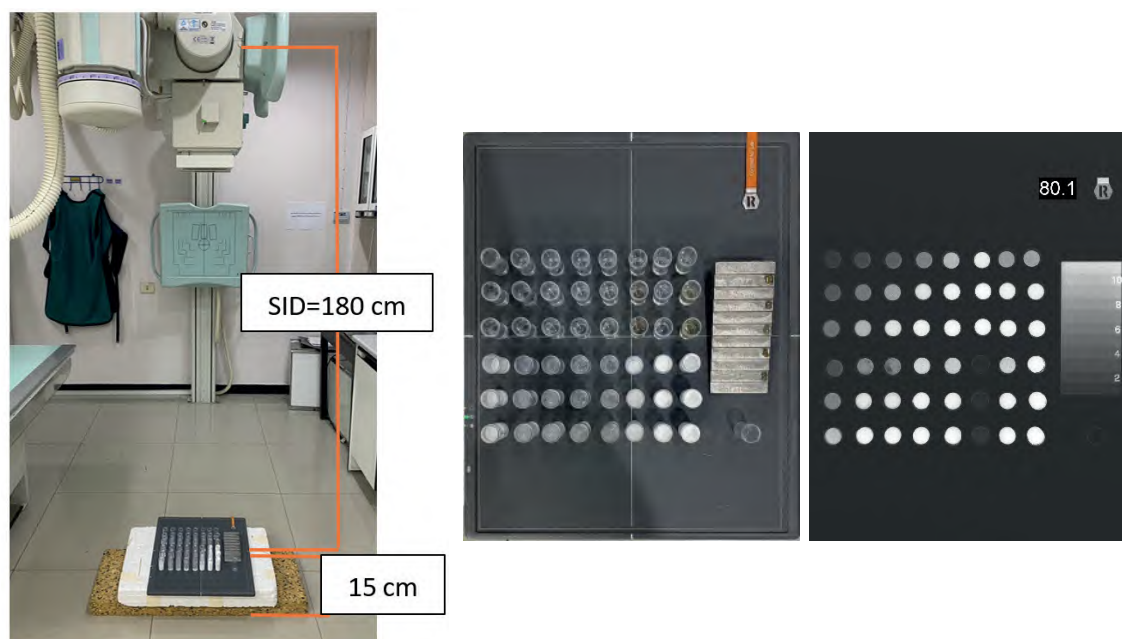


Figure 1. Arrangement of equipment for measuring the initial and transmitted radiation of all materials on the DR plate.

X-ray spectrum measurement

The X-ray spectrum was recorded using a CdTe detector (Amp-Tek XR-100T-CdTe Detector) at the setting energy of 60, 70, 80, 90, 100, and 120 kVp.¹⁰ The detector was previously calibrated using a Ba-133 source with a gain of 3.197 and the number of multichannel analyzers (MCA) at 2048 channels. The detector was set at SID 40 cm to measure the number of X-ray photons as a function of energy (keV) in the condition with and without iodide-starch-gel-based 1 cm.

Results

The physicochemical properties of Iodide-starch-gel-based materials (ISG) were investigated during preparation. The exothermic reaction between mung bean starch (MBS) colloid solution and sodium iodide solution (NaI) causes a gel-like texture of ISG with a pH value range of 5-6. (Figure 2) The homogeneity of ISG, as shown in Table 1, is indicated by a consistent density level of each sample with a CV (coefficient of variation) of less than 10.

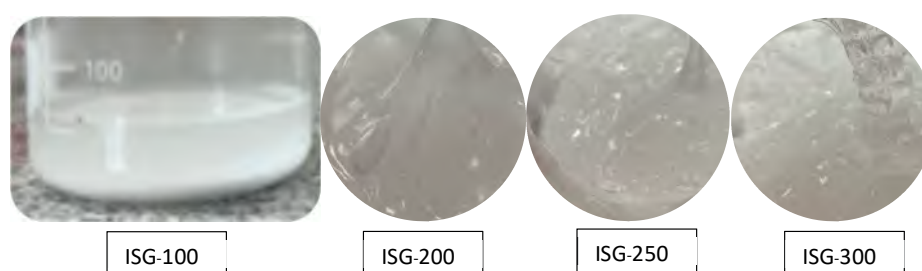


Figure 2. The physical appearance of iodide-starch-gel based material at different concentrations of iodide at 100 (ISG-100), 200 (ISG-200), 250 (ISG-250), and 300 (ISG-300) mg-iodine/gm.

System validation

This study measured the radiation doses (I and I_0) by applying the DR image recording system as a radiation detector that provides a gray-scale image dependable to radiation dose. The radiation dose rate, the uniformity of the DR plate, and the effect produced by the plastic container were verified. The radiation dose of the X-ray was displayed from the X-ray machine in mGy. The radiation property showed a linear proportion of mGy/mAs manner of kVp ($r^2=1$) as shown in Figure 3-left. To check the background and the effect of a clear plastic container on image intensity, the DR plate was irradiated

at various energy settings at 50, 60, 70, 80, 90, and 100 kVp. The radiation dose response on the DR plate was shown as background image intensity. The dose-response curve from the DR plate detector is illustrated in a logistic curve. And the plastic containers showed a slightly reduced image intensity. (Figure 3) The uniformity of the DR plate was investigated from 3 acquired images at 50kVp 2 mAs. The intensity (O.D.) of the region of interest in 6 areas (4 corner locations, 1 middle location, and the whole area) were measured. The mean intensity of the DR plate with the standard deviation (S.D.) equal to 2368 ± 101 , And the %CV was 4.3 (Figure 4)

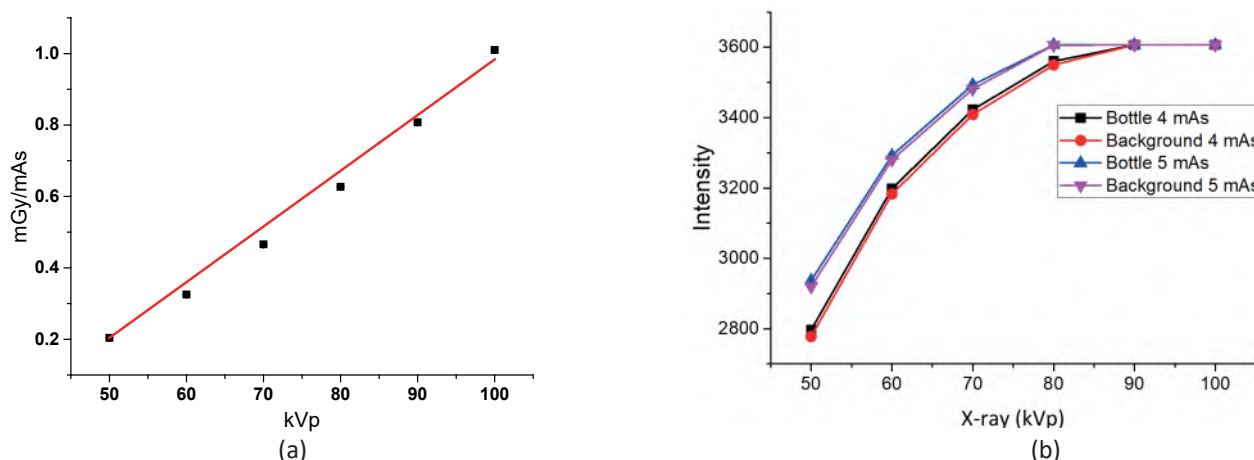


Figure 3. The radiation dose per mAs (mGy/mAs) as a function of kVp, SID 180 cm, 0.5 mm aluminum filter (a), and intensity of plastic container (bottle) and background intensity (b) presented as mean $\pm$ SD (N=2).

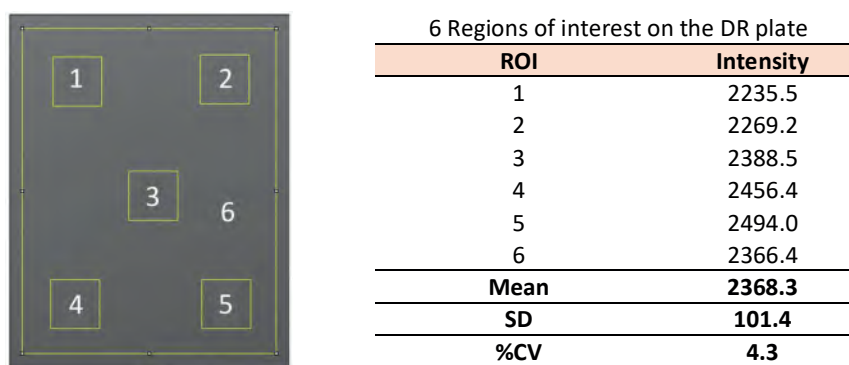


Figure 4. Region of interest (ROI 1, 2, 3, 4, 5, and 6) and intensity value for uniformity evaluation of DR plate.

Linear Attenuation Coefficient

The linear attenuation coefficient of the sample composition consisting of ISG-100, ISG-200, ISG-250, and ISG-300 mg-iodine/gm was calculated from image intensity on the DR plate produced by the transmitted radiation (I) (Table 1). Each energy's initiation radiation (I_0) was estimated using the intensity passed each step of the step-wedge. The sigmoid curve fit extrapolated the initiation radiation value (I_0) as the intensity where step equal to 0 as plotted in Figure 5. Each energy's global

linear attenuation coefficient (kVp setting) was calculated using the Beer-Lambert equation. (Figure 6) The results showed the linear attenuation coefficient of each material was decreased, whereas the exposure technique (kVp) increased. When compared to other substances, the ISG-300 mg-iodine/gm is higher than NaI (300 mg-iodine/gm), BaSO_4 (1:1), omnipaque (300 mg-iodine/mL), and telebrix (350 mg-iodine/mL) at exposure technique 50-100 kVp. (Figure 6)

Table 1. The images relate to various thicknesses (1, 2, and 3 cm) of materials.

Exposure technique setting (4 mAs)	ISG (mg-iodine/gm)												MBS	Nal (mg-iodine/gm)									Contrast media		
	100			200			250			300				100			200			300			BaSO ₄	OM	TE
Thickness (cm)	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	1	1	
50 kVp																									
60 kVp																									
70 kVp																									
80 kVp																									
90 kVp																									
100 kVp																									

Note: ISG: iodide-starch-gel based, MBS: mung bean starch, Nal: sodium iodide solution, BaSO_4 : barium sulfate, OM: omnipaque, TE: telebrix.

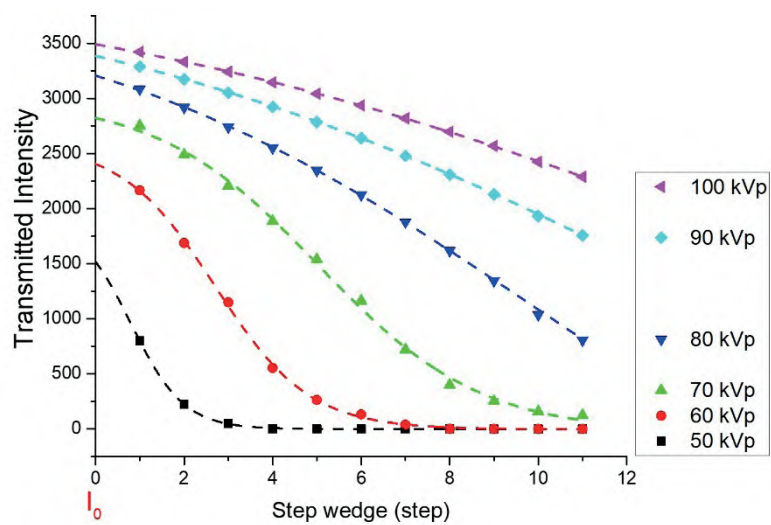


Figure 5. Initiation radiation (I_0) estimation using transmitted intensity from a step wedge.

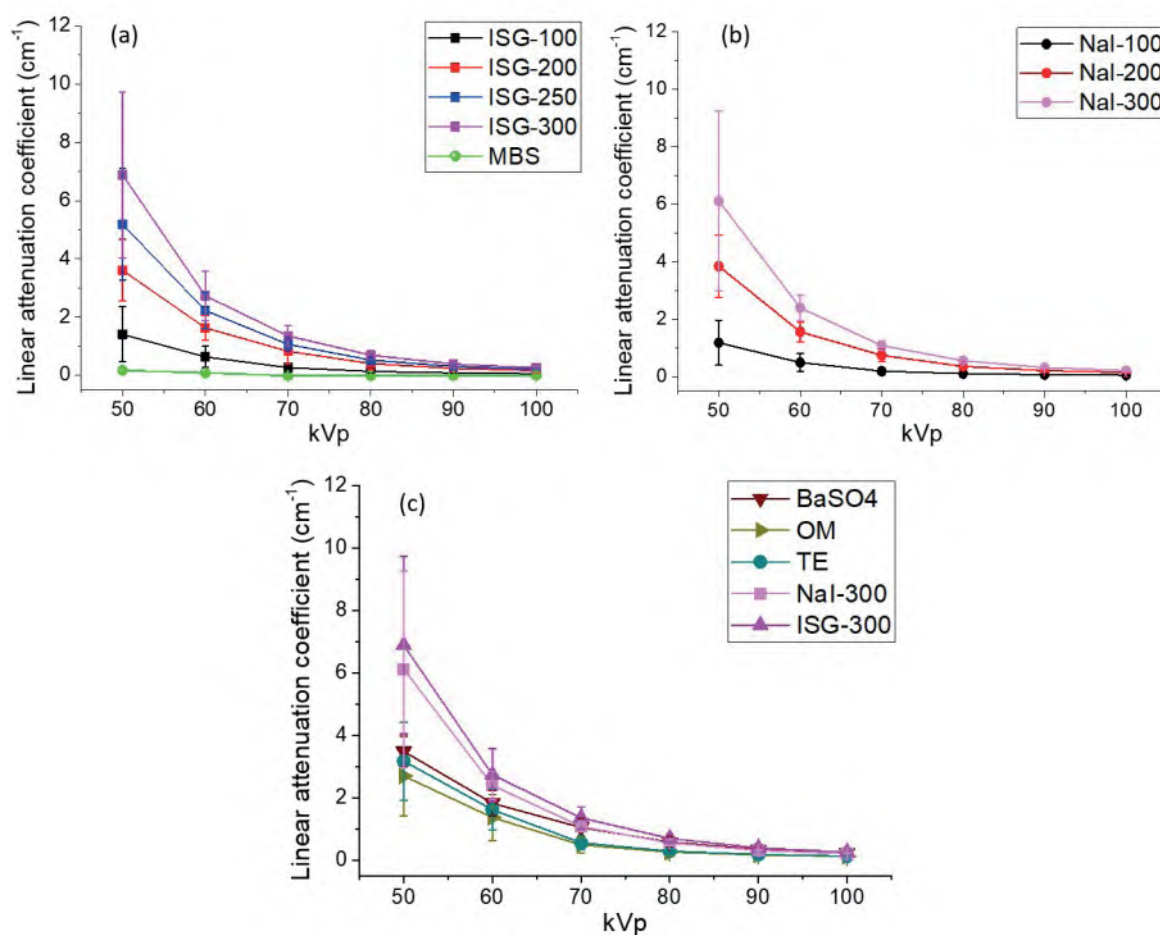


Figure 6. X-ray linear attenuation coefficient (mean $\pm$ SD) of various materials.

X-ray spectrum

The radiation property of X-ray was investigated by recording the photon spectrum that presents photon profiling as a function of energy (keV). The X-ray spectrum illustrated the photon profiling of each setting energy (kVp) of initiation radiation (I_0) and transmitted radiation penetrating through ISG-300. The result showed that ISG-300 efficiently attenuates the X-ray radiation compared with the initiation radiation. The linear attenuation

coefficient profile of each energy setting (kVp) calculated from the X-ray spectrum allowed us to identify the K-edge of ISG, which covers a broad-spectrum range of 30.1-40.5 keV. (Figure 7) Iodine appears to be the main element responsible for this K-edge value. The half-value layer (HVL) and ten-value layer (TVL) were calculated from the mean value of the linear attenuation coefficient and presented in Table 2.

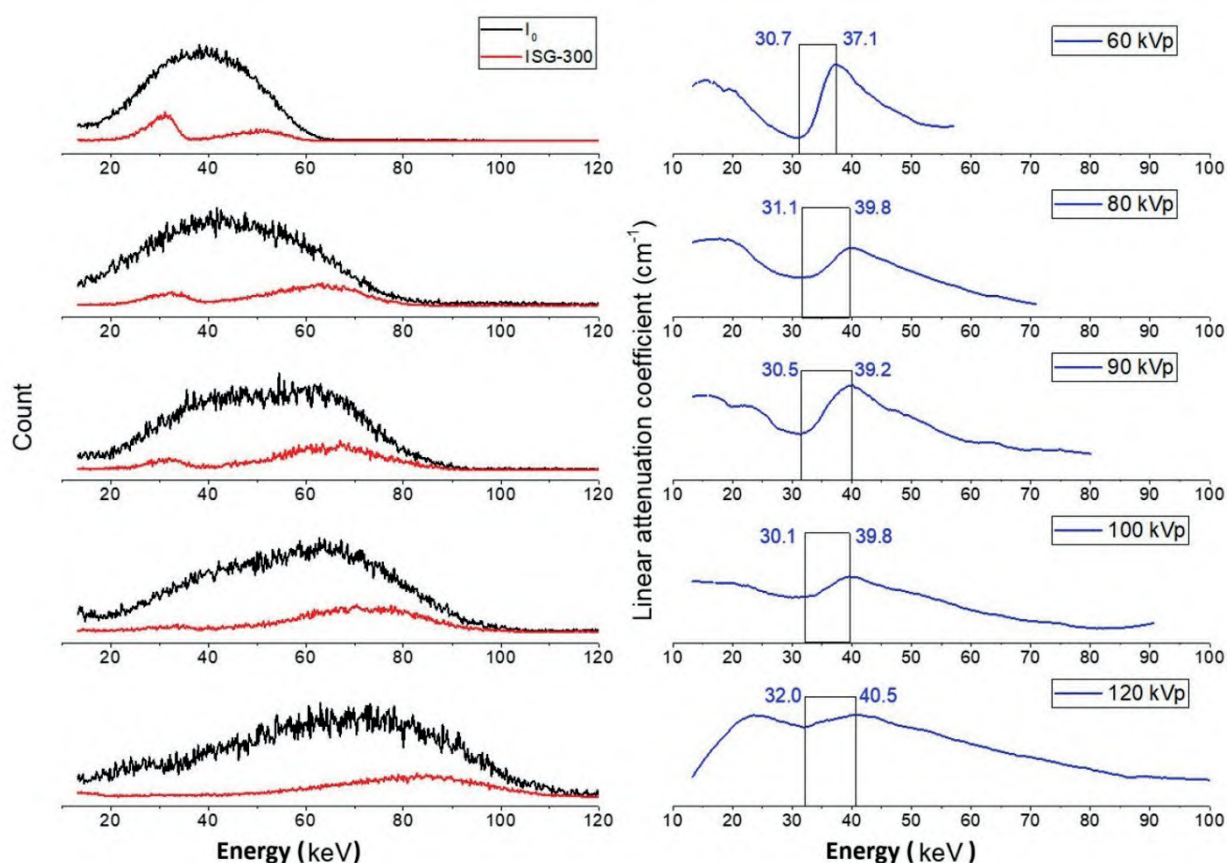


Figure 7. The spectrum of X-ray photon profiling of initiation radiation (black line) and transmitted radiation through iodine-starch-based material (red line) (left), and the linear attenuation coefficient values at setting energy (right).

Table 2. Half value layer (HVL) and ten value layers (TVL) of iodide-starch-gel based (ISG), BaSO₄, omipaque (OM), and telebrix (TE).

kVp	ISG-100	ISG-200	ISG-250	ISG-300	BaSO ₄	OM	TE
Half value layer, HVL (cm)							
50	0.49	0.19	0.13	0.10	0.20	0.26	0.22
60	1.09	0.43	0.31	0.25	0.38	0.51	0.43
70	2.63	0.84	0.65	0.51	0.66	1.44	1.26
80	5.13	1.73	1.33	1.00	1.20	2.70	2.45
90	8.26	2.94	2.29	1.80	2.04	4.19	3.86
100	12.05	4.34	3.39	2.71	3.06	5.95	5.52
Ten value layer, TVL (cm)							
50	1.64	0.64	0.44	0.33	0.66	0.85	0.73
60	3.63	1.41	1.03	0.84	1.26	1.69	1.43
70	8.73	2.79	2.16	1.71	2.21	4.77	4.18
80	17.03	5.75	4.40	3.33	4.00	8.98	8.14
90	27.45	9.76	7.61	5.96	6.78	13.92	12.81
100	40.03	14.41	11.27	9.01	10.17	19.78	18.33

Discussion

Although the study of low-energy X-ray used in mammography on biological effects showed non-significant cellular damage, the increase of double-strand DNA breaks was observed as related to the rise in mutational damage than higher energy X-ray.^{3,11} The iodide-based material is generally used as a contrast agent for diagnostic X-rays. Because of its properties of the K-edge value (33.2 keV) that covers the X-ray spectrum in diagnostic radiation, we herein provide it as a low-energy radiation protection material. Using iodide-based compounds such as NaI with high concentrations causes high toxicity to the body and affects the condition of nausea, vomiting, and peptic ulcer.^{12,13} Therefore, it was developed as an X-ray protection material.

In this study, we invented a radioprotective, iodide-starch-gel-based material that can reduce low-energy X-rays significantly. Moreover, this study simplified a radiation detection system using a DR plate that can be applied to radiation dose detectors in clinical use. Therefore, verifying the X-ray source dose rate and homogeneity of the DR plate is necessary. To apply this detection system, the homogeneity of the DR plate must be verified. The findings indicate that the variability in the homogeneity of the used DR plate (%CV=4.3) was less than 10%, which is within acceptable limits for use as a detector.

This research determined the Linear attenuation coefficient (μ) using 2 methods: 1) a DR plate detection system and 2) a CdTe detector. The radiation dose was determined from the full-energy X-ray spectrum using the DR plate detection system. The resulting μ value reflects the material's attenuation capacity across the entire energy range. The μ value obtained from this method

showed that ISG-300 mg-iodine/gm has more efficiency than the others. The X-ray spectrum acquired by the CdTe detector represents the number of X-ray photons at each energy level (keV) the tungsten target produces. This spectrum enabled the determination of the μ value as a function of energy (keV). The results revealed a reduction in photon intensity, particularly in the 30-40 keV range, when the X-rays passed through the iodide-starch-gel-based material, effectively attenuating low-energy X-rays. Moreover, the linear attenuation coefficient calculated from the X-ray spectrum at each energy (keV) revealed that the μ profile of the ISG-polymer exhibited a broader K-edge spectrum compared to that of the iodine atom alone.

Based on these results, the ISG material is potentially used as X-ray shielding. The critical advantage of iodide-starch-gel-based materials is their ability to self-polymerize through an exothermic reaction, simplifying the preparation process. Additionally, their semi-solid, gel-like nature allows for various functional modifications. These properties suggest that ISG materials can be developed as coatings to attenuate X-rays in diagnostic radiology.^{9,14}

Conclusion

The iodide-starch-gel-based components, derived from mung bean starch combined with a sodium iodide solution, effectively attenuate X-ray radiation in the 30-40 kV range used in diagnostic radiology. With these properties and gel-like consistency, the material shows potential for development as a protective material to reduce X-ray exposure.

Conflict of interest

The authors claim no conflict of interest.

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References

- [1] Aye KT, Wattanapongpitak S, Supawat B, Kothan S, Udomtanakunchai C, Tima S, *et al.* Effect of pre-low-dose irradiation on anticancer activities of gallic acid in leukemic K562 and K562/Dox cells: cell viability and cellular energetic state studies. *Med Oncol.* 2022; 39(12): 229. doi:10.1007/s12032-022-01835-4.
- [2] Supawat B, Homnuan P, Kanthawong N, Semrasa N, Tima S, Kothan S, *et al.* Different responses of normal cells (red blood cells) and cancer cells (K562 and K562/Dox cells) to low-dose (137)Cs gamma-rays. *Mol Clin Oncol.* 2021; 14(4): 74. doi:10.3892/mco.2021.2236.
- [3] Pereira L, Ferreira MT, Lima AGF, Salata C, Ferreira-Machado SC, Lima I, *et al.* Biological effects induced by doses of mammographic screening. *Phys Med.* 2021; 87: 90-8. doi:10.1016/j.ejmp.2021.06.002.
- [4] Smith T, Kearfott KJ. Practical Considerations for Gamma-Ray Spectroscopy with NaI(Tl): A Tutorial. *Health Phys.* 2018; 114(1): 94-106. doi:10.1097/HP.0000000000000804.
- [5] Faucon AL, Bobrie G, Clement O. Nephrotoxicity of iodinated contrast media: From pathophysiology to prevention strategies. *Eur J Radiol.* 2019; 116: 231-41. doi:10.1016/j.ejrad.2019.03.008.
- [6] Wang L, Li Q, Wang XM, Hao GY, Jie B, Hu S, *et al.* Enhanced radiation damage caused by iodinated contrast agents during CT examination. *Eur J Radiol.* 2017;92:72-7. doi:10.1016/j.ejrad.2017.04.005.
- [7] Daowtak K, Pilapong C, Tochaikul G, Moonkum N. Effect of iodinated contrast media on peripheral blood mononuclear cells in terms of cell viability, cell cycle and oxidative stress in an in vitro system. *Toxicol Mech Methods.* 2023; 33(8): 667-74. doi.org/10.1080/15376516.2023.2230486.
- [8] Wang Y, Ding P, Xu H, Li Q, Guo J, Liao X, *et al.* Advanced X-ray Shielding Materials Enabled by the Coordination of Well-Dispersed High Atomic Number Elements in Natural Leather. *ACS Applied Materials & Interfaces.* 2020; 12(17): 19916-26. doi:10.1021/acsami.0c01663.
- [9] Moonkum N, Pilapong C, Daowtak K, Tochaikul G. Radiation Protection Device Composite of Epoxy Resin and Iodine Contrast Media for Low-Dose Radiation Protection in Diagnostic Radiology. *Polymers (Basel).* 2023; 15(2): 430. doi.org/10.3390/polym15020430.
- [10] Hayashi H, Okino H, Takegami K, Kimoto N, Maehata I, Kanazawa Y, *et al.* Experimental evaluation of response functions of a CdTe detector in the diagnostic region with the aim of carrying out a basic experiment concerning a next generation photon counting system. Poster presentation in ECR 2016. doi:10.1594/ecr2016/C-0006.
- [11] Heyes GJ, Mill AJ, Charles MW. Enhanced biological effectiveness of low energy X-rays and implications for the UK breast screening programme. *Br J Radiol.* 2006; 79(939): 195-200. doi:10.1259/bjr/21958628.
- [12] Bulloch MN. Acute iodine toxicity from a suspected oral methamphetamine ingestion. *Clin Med Insights Case Rep.* 2014; 7: 127-9. doi:10.4137/CCRep.S20086.
- [13] Mishkin MM. Contrast media safety; What do we know and how do we know it? *Am J Cardiol.* 1990; 66(14): F34-F6. doi:10.1016/0002-9149(90)90639-i.
- [14] Aral N, Nergis B, Candan C. An alternative X-ray shielding material based on coated textiles. *Text Res J.* 2015; 86(8): 803-11. doi:10.1177/0040517515590409.

Effect of attachment-based family therapy to reduce depression among persons diagnosed with schizophrenia

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ABSTRACT

Background: Schizophrenia is a chronic mental disorder that affects a person's way of thinking, his behaviors, and his or her feelings. One of the common symptoms of schizophrenia is depression, and depression can be associated with suicidal thoughts. Attachment-based family therapy is an intervention that was used to treat depression in young adults but has never been used in persons diagnosed with schizophrenia.

Objective: This study was done to find out the effect of Attachment-based family therapy on reducing depression among persons diagnosed with schizophrenia.

Materials and methods: Thirty male participants aged between 25 and 60 years who were already diagnosed with schizophrenia were selected and participated in this study. The participants were divided into 2 groups, with 15 participants in each as experimental and control groups. Beck's Depression Inventory was used to find out the level of depression in both groups. The experimental group underwent Attachment-Based Family Therapy, whereas the control group attended conventional occupational therapy for 3 months. The SPSS software version was used for data analysis. The descriptive statistics examined the distribution of records to summarize the data. If the $p < 0.05$, it is statistically significant.

Results: The results of this study showed that Attachment-Based Family Therapy was effective in reducing depression among persons diagnosed with Schizophrenia.

Conclusion: The results suggested that Attachment-Based Family Therapy was effective for the experimental group, and the level of depression decreased after the intervention.

Introduction

Mental health is an essential part of society and people's lives. Poor mental health affects people's ability to work, well-being, family, and maintain relationships with friends and the community. Mental health conditions are expected. It's estimated about 1 in 5 men and 1 in 3 women will experience major depression. Other conditions, such as bipolar disorder and schizophrenia, have a significant impact on people's lives, but they are less common. The effects of mental illnesses can be reduced and treatable. Occupational therapy has a considerable influence on the treatment of mental illnesses.¹

Schizophrenia is a chronic, complex mental health disorder characterized by many symptoms, including impaired cognitive ability, disorganized speech or behavior, hallucinations, and delusions. For many patients and their families, it is a disabling disorder due to its early

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onset of the disease, along with its chronic course. There are negative and cognitive symptoms of schizophrenia. Negative symptoms may be characterized by deficits or loss. Cognitive symptoms include impairments in executive functions, attention, and working memory. In addition, relapse may occur because of positive symptoms, such as hallucinations, delusions, and suspiciousness.²

Previous evidence suggests that people with schizophrenia not only have psychosocial risks but also biological illnesses that accompany relapse. Early identification and early intervention will reduce the risk of relapse, reduce disease burden, and improve schizophrenic patient outcomes in the long term.³

Depression is one of the leading causes of disability worldwide, and feelings of loneliness contribute significantly to depression.⁴ Depression is associated with reduced quality of life and significant functional impairment. Specific functional areas such as work, cognitive function, and interpersonal relationships can be disrupted due to depression.⁵

The World Health Organization (WHO) and Global Burden of Disease Study ranked depression as the single most burdensome disease in the world in terms of total disability-adjusted life years among people in midlife due to the rates of depression being so high. It is also a highly recurrent disorder.⁶

An elevated risk for developing depressive symptoms has been found in schizophrenia patients compared to the lifetime prevalence of depression in the general population. An increased risk of suicide is associated with the course of schizophrenia, and depressive symptoms have been reported during all stages of schizophrenia. Certain depressive symptoms and negative symptoms of schizophrenia showed an overlap. For example, abulia, motivation, social withdrawal, alogia, anhedonia, and avolition status. The pathophysiology and etiology of both depression and schizophrenia remain poorly understood. There is some relationship between the two disorders, which affects the severity of both disorders.⁷

Attachment-based family therapy (ABFT) is a problem-solving approach to the treatment of adolescent depression, trauma, and suicidality, and ABFT is based on attachment theory. ABFT provides a clear and structured roadmap to help therapists quickly address the underlying problems at the heart of family conflict, even if they are structural. Therapists try to uncover experiences and relational processes that prevent adolescents from reaching out to their parents for help when they are suicidal—learning skills in reflection and emotion regulation under the influence of attachment security. For example, children turn to their caregivers for care and comfort when they are afraid or insecure. Over time, self-regulation skills come into play because of the caregiver's many experiences helping the child to reduce his or her fears. In addition to the psychological stress of self-care, the caregiver's responsibility allows children to live independently. Maintaining relationships while choosing independence is the first step of adolescence, not isolation and individuality. Youth who maintain this

balance have fewer peer relationships, do better in school, and show better health outcomes. Adolescents are less skilled at interpersonal problem-solving and emotional regulation if they do not have a supportive parenting environment. A lack of these skills increases the risk of many mental illnesses, including suicide and depression.⁸ Attachment-based family therapy has proven to be an effective treatment intervention for depression. There are many intervention strategies used to reduce depression in schizophrenia. Still, there have been fewer studies done to find the effect of attachment-based family therapy on reducing depression among persons diagnosed with schizophrenia.

Hence, this study has been done to find out the effect of attachment-based family therapy on reducing depression among persons diagnosed with schizophrenia.

Materials and methods

Study design

A Quasi-experimental study design was used in the study to find out the effect of Attachment-Based Family Therapy on reducing depression among persons diagnosed with schizophrenia. A convenient sampling technique was used. A total of 30 subjects were selected and divided into two groups 15 in the control group 15 in the experimental group. Samples were collected in Rehabilitation setups that are Confident Health Centre - Maduravoyal, Chennai, and Helping Hearts – Oragadam, Chennai.

Participants

Participants were selected according to the inclusion and exclusion criteria. Persons diagnosed with schizophrenia with depression, People aged between 25 and 60, only male patients, and patients with all levels of depression were included. Persons diagnosed with other conditions, people aged below 25 and above 60, and patients with other co-morbid conditions other than depression were excluded. Participants were asked to give their written consent and submitted their consent to participate in this study.

Instrument

The Beck's Depression Inventory (BDI) was used in this study. The BDI is a self-reporting questionnaire that has 21 items that help to evaluate the severity of depression in psychiatric and normal populations. The Beck's Depression Inventory is a 4- 4-point scale from 0 (symptom absent) to 3 (severe symptoms). 0 is the minimum score, and 63 is the maximum score. Scores of 0-13 indicate minimal depression, 14-19 indicate mild depression, 20-28 indicate moderate depression, 29-63 indicate severe depression. The reliability and validity of the scale are as follows. The internal consistency of Beck's depression inventory is 0.9. Range from 0.73 to 0.96 was the test-retest reliability of Beck Depression Inventory. 0.72 and 0.60 have been found as Mean correlation coefficients between clinical ratings of depression and the BDI for the population. Between Beck's Depression Inventory and other measures of depression, such as the Minnesota Multiphasic Personality

Inventory-D, $r=0.77$ has demonstrated high concurrent validity.

Procedure

In this study, a total of 30 participants diagnosed with schizophrenia who are also suffering from depression were selected and divided into two groups. Fifteen participants in the experimental groups and 15 participants in the control group were placed. In Attachment-based family therapy, five treatment tasks were used in the experimental group. Task one focuses on getting family members to engage in a treatment focused on relationship building rather than behavioral management. It focuses on promoting caregivers to help the patient cope with and recover from depression. Task two consists of individual sessions with patients. Task three consists of individual sessions with the caregivers. It helps caregivers consider how their life stressors and intergenerational legacies of attachment affect their ability to connect better with their family. In task four, the patient and the caregiver come back together to discuss how rational disappointments have damaged trust in the relationship. Then, task five focuses on using caregivers to support the patient's exploration of competency and autonomy. The control group received conventional occupational therapy. The study duration was 3 months, 3 days a week, and 45 minutes per session.

Data analysis

A Quasi-experimental study was carried out by analyzing the inferential studies in this study. Mean and standard deviation (Minimum-Maximums) were repeatedly measurement criteria for the results. The SPSS software version was used for data analysis. The descriptive statistics examined the distribution of records

to summarize the data. If the $p < 0.05$, it is statistically significant. Since the samples belonged to the sample size (30), a non-parametric method was used to test the statistical differences between pre-test and post-test scores of the control and experimental groups. The Wilcoxon signed-rank test and Mann-Whitney U test were analyzed to find the hypothesis being tested and identify whether a statistically significant difference exists in consideration of the treatment given. An alpha level of $p=0.05$ was measured to be statistically significant. The statistical analysis was done with the help of IBMSPSS version 23.0

Results

Table 1 shows the statistical difference between the pre-test and post-test in the control group, which was measured with the BDI. The mean value of the post-test is 30.06, which is less than the mean value of the pre-test of the control group. The p -value is 0.001, which is lower than 0.05. Hence, there is a statistically significant difference between the pre-test and post-test scores in the Control Group. This suggests that the conventional occupational therapy intervention the control group received significantly improved.

Table 2 shows the statistical difference between the pre-test and post-test in the experimental group, which was measured with the BDI. The mean value of the post-test is 22.66, which is less than the mean value of the pre-test of the experimental group. The p is 0.001, which is lower than 0.05. Hence, there is a statistically significant difference between the pre-test and post-test scores in the experimental group. This suggests that the Attachment-Based Family Therapy intervention received by the experimental group had significant improvement.

Table 1. Mean differences between the control group.

Group	Mean	SD	N	Z value	p value
Control group (pre-test)	32.93	8.85	15	-3.458	0.001*
Control group (post-test)	30.06	8.37	15		

Note: *Significant at 5% alpha level.

Table 2. Mean differences between the experimental group.

Group	Mean	SD	N	Z value	p value
Experimental group (pre-test)	33.86	5.70	15	-3.417	0.001*
Experimental group (post-test)	22.66	5.70	15		

Note: *Significant at 5% alpha level.

Table 3 shows the statistical difference between the post-tests of the control and experimental groups, measured with the BDI. The mean value of the experimental group's post-test is less than the mean value of the post-test of the control group. The p is 0.015, which is lower than

0.05. Hence, there is a statistically significant difference between post-test scores in the control and experimental group. This suggests that the attachment-based family therapy intervention received by the experimental group had significant improvement.

Table 3. Mean differences between the post-test scores of the control and the experimental groups.

Group	Mean	SD	N	Z value	p value
Control group (post-test)	30.06	8.37	15	2.405	0.015*
Experimental group (post-test)	22.66	5.70	15		

Note: *Significant at 5% alpha level.

Discussion

The purpose of this study was to examine the effect of attachment-based family therapy on reducing depression among persons diagnosed with schizophrenia. This study was conducted for 3 months with 36 sessions.

In Table 1, the control group exhibited a statistically significant difference ($p=0.001$), with their mean score decreasing from 32.93 at the pre-test to 30.06 at the post-test. These findings suggest that the intervention received by the control group positively impacted depression reduction, as measured by the BDI. These findings were supported by a Quasi-experimental study conducted by Emel Bahadır Yilmaz. In this study, they did a non-randomized control group pre-test, post-test, and follow-up design. The group mindfulness-based cognitive therapy program was an intervention for 82 second-year undergraduate nursing students. With the test results, the study concluded that mindfulness-based cognitive therapy programs conducted with nursing students influenced students' mindful attention awareness and stress levels and reduced the levels of depression, which stated that the conventional occupational therapy received by the control group was effective in reducing depression.⁹

In Table 2, the experimental group demonstrated a highly statistically significant difference ($p=0.001$), in their mean score, from 33.86 in the pre-test to 22.66 in the post-test. This improvement indicates that the attachment-based family therapy that the experimental group received was effective in reducing depression, as measured by BDI. These findings were supported by an exploratory study done by Roger Kobak, and the results revealed that attachment-based family therapy that the LGBQ adolescents receive showed a greater rate of reduction in depressive symptoms ($p<0.001$), which stated that the Attachment-Based Family Therapy intervention helps reduce depression.¹⁰

In Table 3, when comparing the post-test scores between the groups, the experimental group exhibited a significantly lower mean score of 22.66 compared to the control group's mean of 30.06 ($p=0.015$). These findings suggest that the ABFT intervention received by the experimental group was more effective than the control group's conventional occupational therapy intervention in reducing depression among individuals with schizophrenia. A randomized controlled trial supported these findings, and the results demonstrated significantly greater rates

of change in depression in patients receiving Attachment-Based Family Therapy.¹¹

Conclusion

Attachment-based family therapy aims to help individuals with behavioral and mental health problems, especially depression and suicide. This also helps improve individuals' emotional regulation, problem-solving, interpersonal skills, and the quality of interaction between people. Thirty individuals with Schizophrenia ($N=30$) were selected 15 participants were assigned to the control group, and 15 participants were assigned to the experimental group. The experimental group received Attachment-Based Family Therapy, and the control group received conventional occupational therapy. Post-test scores were measured using BDI. Further analysis revealed that attachment-based family therapy was more effective on depression among persons diagnosed with schizophrenia than traditional occupational therapy.

Limitations and recommendations

The study was done with a small sample size, for a shorter duration of time, in a confined age group, and only with male patients.

A study can be done with a larger sample size, for a longer duration of time, or by including both genders.

Conflict of interest

No conflict of interest.

Ethical approval

This study has been approved by the Institution Scientific Review Board (ISRB) of Saveetha College of Occupational Therapy with REF.NO of SCOT/ISRB/046/2023.

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References

- [1] Dattani S, Rodes-Guirao L, Ritchie H, Roser M. Mental health. Our World in Data. 2023. Published online at Our World in Data. Org.
- [2] Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. PT. 2014; 39(9): 638-45. PMID: PMC4159061, PMID: 25210417
- [3] Newton R, Rouleau A, Nylander AG, Loze JY, Resemann HK, Steeves S, Crespo-Facorro B. Diverse definitions of the early course of schizophrenia—a targeted literature review. NPJ Schizophrenia. 2018; 4(1): 21. doi: 10.1038/s41537-018-0063-7.
- [4] Tsai HH, Cheng CY, Shieh WY, Chang YC. Effects of a smartphone-based videoconferencing program for older nursing home residents on depression, loneliness, and quality of life: a quasi-experimental study. BMC Geriatrics. 2020; 20: 27. doi.org/10.1186/s12877-020-1426-2
- [5] Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional: Recovery from depression. CNS Drugs. 2010; 24: 267-84. doi: 10.2165/11530230-000000000-00000
- [6] Garber J, Horowitz JL. Depression in children. Handbook of depression. 2002: 510-40.
- [7] Salleh MR. The genetics of schizophrenia. Malays J Med Sci. 2004; 11(2): 3-11. PMID: PMC3433970, PMID: 22973121
- [8] Diamond G, Diamond GM, Levy S. Attachment-based family therapy: Theory, clinical model, outcomes, and process research. Journal Affect Disord. 2021; 294: 286-95. doi: 10.1016/j.jad.2021.07.005.
- [9] Yüksel A, Yılmaz EB. The effects of group mindfulness-based cognitive therapy in nursing students: A quasi-experimental study. Nurse Educ Today. 2020; 85: 104268. doi: 10.1016/j.nedt.2019.104268
- [10] Russon J, Abbott CH, Jin B, Rivers AS, Winston-Lindeboom P, Kobak R, Diamond GS. Attachment-based family therapy versus nondirective supportive therapy for lesbian, gay, bisexual and questioning adolescents with depression, and suicidal ideation: An exploratory study. Suicide Life Threat Behav. 2023; 53(6): 958-67. doi: 10.1111/sltb.12995
- [11] Rognli EW, Waraan L, Czajkowski NO, Aalberg M. Moderation of treatment effects by parent-adolescent conflict in a randomised controlled trial of Attachment-Based Family Therapy for adolescent depression. Scand Child Adolesc Psychiatr Psychol. 2020; 8(1): 110-22. doi: 10.21307/sjcapp-2020-011

Review article: Local medicinal plants in Nigeria for the management of diabetes; an evaluating of glucose metabolism, insulin sensitivity, and physiological parameters

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ABSTRACT

Background: Nigeria, like many regions worldwide, faces a growing burden of diabetes, prompting increased interest in traditional medicinal practices.

Objective: This review examines the efficacy of local medicinal plants in Nigeria for managing diabetes mellitus, focusing on their effects on glucose metabolism, insulin sensitivity, and physiological parameters.

Materials and methods: Four commonly used plants, Aloe vera, bitter leaf (*Vernonia amygdalina*), bitter lemon (*Citrus aurantium*), and ginger (*Zingiber officinale*), were scrutinized for their potential therapeutic effects.

Results: The literature review revealed numerous studies exploring the antidiabetic properties of these plants, including their ability to lower blood glucose levels, improve insulin sensitivity, and modulate various physiological parameters associated with diabetes.

Conclusion: The findings suggest promising avenues for utilizing local medicinal plants in diabetes management, although further research, including clinical trials, is warranted to validate their efficacy and safety.

Introduction

Diabetes is a chronic metabolic disorder characterized by high blood glucose levels caused by impaired insulin synthesis, action, or both. This disease has become a primary global health concern, affecting millions of people around the world. According to the International Diabetes Federation (IDF), around 463 million persons had diabetes in 2019, with this figure expected to climb to 700 million by 2045.¹ Diabetes prevalence is impacted by several factors, including genetics, age, ethnicity, and lifestyle choices.² While genetic predisposition is essential in diabetes development, lifestyle variables have emerged as significant predictors of its onset and progression.^{3,4} A Sedentary lifestyle, poor eating habits, and obesity have all been linked to an increased risk of acquiring type 2 diabetes.^{5,6} Furthermore, physical inactivity contributes significantly to the increased prevalence of diabetes. Sedentary behavior and a lack of regular physical activity have been associated with insulin resistance, poor glucose metabolism, and an increased risk of developing type 2 diabetes.⁷ Understanding the physiological changes due to diabetes is critical for creating tailored therapies.

Insulin, a hormone released by the pancreas, is vital in controlling blood glucose levels. In people with type 1

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diabetes, the pancreas fails to produce insulin, resulting in uncontrolled hyperglycemia. Type 2 diabetes, on the other hand, is distinguished by insulin resistance, in which the body's cells become less receptive to insulin action. Insulin resistance is frequently associated with reduced insulin secretion.

Diabetes has far-reaching systemic consequences in addition to its effects on glucose metabolism. Chronic hyperglycemia can result in both microvascular and macrovascular repercussions, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. Oxidative stress, inflammation, and endothelial dysfunction are the underlying causes.⁸

Despite advancements in medical interventions, managing diabetes remains a significant challenge. While conventional treatment options such as insulin therapy and oral hypoglycemic agents are available, they may be associated with adverse effects and limited efficacy.⁹ Therefore, there is a need to explore alternative approaches to diabetes management. This review aims to investigate the potential use of some selected medicinal plants in diabetes management and evaluate their effects on glucose control, insulin sensitivity, and other relevant physiological parameters.

This review will contribute to the growing knowledge of using medicinal plants in diabetes management, which may provide additional treatment options for individuals with diabetes. Secondly, investigating bioactive compounds and their mechanisms of action can shed light on the physiological pathways involved in glucose regulation, potentially leading to developing novel therapeutic approaches. Additionally, evaluating potential side effects or adverse reactions associated with medicinal plant extracts will provide valuable insights into their safety profile.

This review justifies the need for alternative and complementary approaches to diabetes management. Conventional treatment options for diabetes have limitations, including side effects and variable efficacy. Medicinal plants in diabetes management offer a potential avenue for developing safer and more effective therapeutic interventions. By exploring the impact of medicinal plant extracts on glucose control, insulin sensitivity, and related physiological parameters, this review will provide scientific evidence for their potential utility in diabetes management, ultimately benefiting individuals with diabetes and healthcare providers seeking additional treatment options.

Medicinal plants

Medicinal plants have been used in traditional medicine systems for centuries to manage diabetes. These plants contain bioactive compounds that may exert anti-diabetic effects by various mechanisms, including enhancing insulin secretion, improving insulin sensitivity, and reducing postprandial glucose levels.¹⁰ Research on medicinal plants for diabetes management has gained momentum recently. Studies have investigated the bio-active compounds present in these plants, their

mechanisms of action, and their potential as adjuvant therapy in diabetes management.^{2,10}

Medicinal plants with anti-diabetic activities

Aloe vera

Aloe vera (*Aloe barbadensis miller*) is a widely recognized medicinal plant used for centuries in traditional medicine systems. Its gel, extracted from the leaves, contains various bioactive compounds that have shown potential in managing diabetes mellitus.

Traditional use of aloe vera

1. Wound healing: Aloe vera has long been recognized for its wound-healing properties. The aloe vera leaf gel contains polysaccharides, such as acemannan, which have been shown to accelerate wound healing by promoting collagen synthesis and enhancing the proliferation of fibroblasts.¹¹ The gel can be topically applied to minor burns, cuts, and abrasions to promote healing and reduce inflammation.¹²

2. Skin conditions: Aloe vera has been used traditionally to alleviate various skin conditions, including sunburn, psoriasis, and dermatitis. The aloe vera gel possesses anti-inflammatory and moisturizing properties, which can help soothe irritated skin and reduce redness.¹³ It may also aid in the regeneration of skin cells and the repair of damaged tissues.¹¹ Topical application of aloe vera gel is effective in reducing the symptoms of psoriasis and improving the overall condition of the skin.^{14,15}

3. Digestive health: Aloe vera has a long history of use in traditional medicine for digestive ailments, including constipation, indigestion, and irritable bowel syndrome (IBS). The aloe vera gel contains anthraquinone compounds, such as aloin, which have laxative properties and can help relieve constipation.¹⁶ Additionally, aloe vera gel has been shown to have anti-inflammatory effects on the digestive tract, which may benefit individuals with IBS or inflammatory bowel disease.¹⁷

4. Immune system support: Aloe vera has been traditionally used to support immune function. The aloe vera gel contains bioactive compounds, including polysaccharides and antioxidants, which have immunomodulatory effects.¹⁸ These compounds can enhance the activity of immune cells and promote the production of antibodies, thus supporting the body's defense against pathogens.¹¹

Aloe vera bioactive compounds and mechanisms of action

Aloe vera gel contains several bioactive compounds, including polysaccharides, anthraquinones, flavonoids, and phytosterols. These compounds are believed to contribute to the plant's therapeutic properties in diabetes management.

Polysaccharides present in aloe vera, such as acemannan, have been shown to possess immunomodulatory and anti-inflammatory effects. They may help improve insulin sensitivity by reducing chronic low-grade inflammation, often associated with insulin resistance.¹⁹ Additionally, polysaccharides may stimulate insulin release

from pancreatic beta cells, promoting glucose uptake by peripheral tissues.¹¹

Anthraquinones, such as aloin and emodin, found in aloe vera, have exhibited antioxidant and anti-inflammatory properties. These compounds may help protect pancreatic beta cells from oxidative stress and inflammation, preserving their function and insulin production.¹⁹

Flavonoids in aloe vera, including quercetin and kaempferol, possess antioxidant and anti-inflammatory activities.²⁰ They may improve insulin sensitivity by reducing oxidative stress and inflammation in insulin-target tissues.²¹

Phytosterols, such as beta-sitosterol, are plant-derived compounds found in aloe vera. They have been shown to enhance insulin sensitivity by modulating cellular signaling pathways involved in glucose metabolism.²²

Aloe vera impact on insulin sensitivity and insulin secretion

Studies have investigated the impact of aloe vera extracts on insulin sensitivity and secretion. Animal and *in vitro* studies have shown that aloe vera gel or its components can improve insulin sensitivity by enhancing glucose uptake and utilization in peripheral tissues.^{11,19} Aloe vera extracts have also been reported to stimulate insulin secretion from pancreatic beta cells, potentially contributing to improved glycemic control.¹¹

However, it is essential to note that human clinical trials investigating the effects of aloe vera on insulin sensitivity and insulin secretion in individuals with diabetes are limited. Further research is necessary to establish aloe vera supplementation's specific dosage, duration, and efficacy in improving human insulin sensitivity and secretion.

Previous studies on the anti-diabetic effect of aloe Vera

Dede *et al.* studied Aloe vera's antihyperglycemic and histological effects in an alloxan-induced diabetic Wistar rat model.²⁰ Their findings showed that 100 mg/kg, 200 mg/kg, and 400 mg/kg of aloe vera dramatically lowered blood glucose levels dose-dependently. In an alloxan-induced diabetic Wistar rat model, aloe vera displayed antihyperglycemic effects and retained organ histology, indicating its promise as an alternative or complementary therapy for diabetes control.

Also, Arora *et al.* evaluated the effect of aloe vera on diabetes-induced nephropathy in rats in another investigation.²¹ Streptozotocin (STZ) (55 mg/kg intraperitoneally once) was given to rats to establish experimental diabetes mellitus. Treatment with aloe vera (300 mg/kg/day orally) was found to be more effective against diabetes-induced nephropathy and renal oxidative stress than the reference drug, lisinopril (1 mg/kg/day orally). Aloe vera (300 mg/kg/day orally) medication may have averted the development of diabetes-induced nephropathy by lowering lipid levels, reducing renal oxidative stress, and providing a direct renoprotective effect.²¹

Potential side effects or adverse reactions of aloe vera

While aloe vera is generally considered safe for topical use and ingestion in moderate amounts, there have been reports of potential side effects and adverse reactions associated with its use for diabetes management.²²

Oral aloe vera extracts may cause gastrointestinal disturbances, such as diarrhea, abdominal cramps, and electrolyte imbalances.²³ Prolonged and excessive use of aloe vera can also lead to a laxative effect due to the presence of anthraquinones, which may result in electrolyte depletion and dehydration.²³

Furthermore, individuals who are on medication for diabetes or other medical conditions should exercise caution when using aloe vera extracts, as they may interact with certain medications, affecting their efficacy or increasing the risk of adverse effects.²³

Bitter leaf

Bitter leaf (*Vernonia amygdalina*) is a plant widely recognized for its medicinal properties and is commonly used in traditional African medicine systems. It belongs to the Asteraceae family and is known by various names, including "Onugbu" in Igbo and "Ewuro" in Yoruba. Due to its bioactive compounds and therapeutic properties, bitter leaf has gained attention for its potential role in managing diabetes mellitus.

Traditional use of bitter leaf

1. Digestive health: Bitter leaf has been traditionally used to support digestive health and alleviate gastrointestinal issues. It is known for its bitter taste, which stimulates the production of digestive enzymes and promotes healthy digestion.²⁴ Bitter leaf extracts have been found to possess antidiarrheal properties and can help reduce the frequency and severity of diarrhea.^{24,25}

2. Fever and malaria: Bitter leaf has been used traditionally to manage fever and malaria. Studies have shown that bitter leaf extracts possess antipyretic properties and can help reduce body temperature during fever. Bitter leaf extracts have also exhibited antimalarial activity against *Plasmodium falciparum*, the parasite responsible for malaria.²⁶

3. Diabetes management: Bitter leaf has been traditionally used to regulate blood sugar levels and manage diabetes. Research has shown that bitter leaf extracts can lower blood glucose levels by enhancing insulin secretion and sensitivity. Bitter leaf extracts have also demonstrated antioxidant properties, which can help protect against oxidative stress associated with diabetes.^{27,28}

4. Anti-inflammatory and antioxidant effects: Bitter leaf contains bioactive compounds, including flavonoids and phenolic compounds, with anti-inflammatory and antioxidant properties. These properties contribute to its traditional use for inflammation-related conditions, such as arthritis and rheumatism. In experimental studies, Bitter leaf extracts inhibit inflammatory mediators and reduce oxidative stress.²⁹

Bitter leaf bioactive compounds and mechanisms of action

Bitter leaf contains diverse bioactive compounds that contribute to its medicinal properties. Some essential compounds identified in bitter leaves include sesquiterpene lactones, flavonoids, alkaloids, phenolic compounds, and steroids.

Sesquiterpene lactones, such as vernodalin and vernolide, are prominent bioactive compounds in bitter leaves. These compounds possess anti-inflammatory, antioxidant, and immunomodulatory properties. They have been reported to inhibit the production of pro-inflammatory cytokines, which could contribute to the prevention of chronic low-grade inflammation often associated with insulin resistance.³⁰

Flavonoids, including luteolin and quercetin, are present in bitter leaves and exhibit antioxidant and anti-inflammatory effects. These compounds have been shown to enhance insulin signaling, improve glucose uptake, and protect pancreatic beta cells from oxidative stress.^{31,32}

Alkaloids, such as vernonioside B1, are bioactive compounds in bitter leaves. They have demonstrated hypoglycemic effects and may contribute to improving insulin sensitivity.³³

Phenolic compounds, such as caffeic acid and chlorogenic acid, possess antioxidant properties and may help reduce oxidative stress in diabetes. They have also shown potential in modulating glucose metabolism and insulin sensitivity.^{31,32}

Steroids, including beta-sitosterol, have been identified in bitter leaf and may contribute to its antidiabetic effects. Beta-sitosterol has been reported to enhance insulin sensitivity and improve glucose uptake in peripheral tissues.³²

Bitter leaf impact on insulin sensitivity and insulin secretion

Research has investigated the impact of bitter leaf extracts on insulin sensitivity and secretion. Animal and in vitro studies have shown that bitter leaf extracts can improve insulin sensitivity by enhancing glucose uptake in skeletal muscle and adipose tissue.³² These extracts have also been reported to stimulate insulin secretion from pancreatic beta cells, potentially contributing to improved glycemic control.³²

Previous studies on the anti-diabetic effect of bitter leaf

Vernonia amygdalina aqueous leaf extract was studied for its hypoglycemic impact in diabetic rats by Johnbull et al.³⁴ Over seven days, normal and diabetic rats were given three doses of the extract (100, 200, and 400 mg/kg). The 400 mg/kg dose reduced fasting blood sugar levels from 494.83 mg/dL to 81 mg/dL, the 200 mg/kg dose decreased levels from 382.33 mg/dL to 98 mg/dL, and the 100 mg/kg dose brought levels down to 110 mg/dL. The extract also substantially affected rats' body weight and other biochemical and hematological parameters, suggesting its potent hypoglycemic activity.

Nwaoguikpe et al.³⁵ investigated the effect of bitter leaf extract (*Vernonia amygdalina*) on blood glucose levels in diabetic rats. *Vernonia amygdalina* (bitter leaf) plant

extract was given to rats orally at doses of 2%, 4%, 6%, 8%, and 10% before meals for 5, 10, and 15 days, respectively, after which blood samples were collected and analyzed for glucose levels using enzymatic methods. Blood glucose levels dropped dramatically from a mean of 4.44 0.2 mmol/L to 1.66 0.2 mmol/L. The reduction in blood glucose levels seen in rats after administration of the plant extract implies that the plant extract has anti-diabetic, anti-hyperglycemic, and hypoglycemic actions on alloxan-induced diabetic rats.

Potential side effects or adverse reactions of bitter leaf

Bitter leaf is generally considered safe for consumption when used in moderate amounts. However, there are potential side effects and precautions to consider. Bitter leaves may cause gastrointestinal discomfort in some individuals, including abdominal pain, diarrhea, or nausea.³² It is important to note that individual tolerances may vary, and everyone does not experience these side effects.

Bitter leaf extracts have been reported to have uterine stimulant effects and may induce contractions. Therefore, pregnant women should avoid the excessive consumption of bitter leaves.³⁴

Bitter melon

Bitter melon (*Momordica charantia*), also known as bitter gourd or karela, is a tropical vine that belongs to the Cucurbitaceae family. It is widely cultivated and consumed in various parts of the world, including Asia, Africa, and the Caribbean. Bitter melon is renowned for its medicinal properties and has been traditionally used for centuries to manage various health conditions, including diabetes mellitus.³⁵

Traditional use of bitter melon

1. Blood sugar regulation: Bitter melon has been traditionally used to help regulate blood sugar levels and manage diabetes. Research has shown that bitter melon extracts contain bioactive compounds, including charantin, polypeptide-p, and vicine, which possess hypoglycemic properties.¹⁰ These compounds have been found to increase insulin sensitivity, stimulate glucose uptake, and inhibit glucose production in the liver.^{36,37}

2. Digestive health: Bitter melon has traditionally been used to support digestive health and alleviate gastrointestinal issues. It has been reported to possess anti-ulcer properties and can help protect the gastric mucosa from damage. Bitter melon extracts have also demonstrated anti-inflammatory effects in the gastrointestinal tract, which may help reduce symptoms of inflammatory bowel disease.^{38,39}

3. Antioxidant and anti-inflammatory effects: Bitter melon contains various bioactive compounds, including flavonoids, phenolic compounds, and triterpenoids, which possess antioxidant and anti-inflammatory properties.⁴⁰ These properties contribute to its traditional use as an anti-aging remedy and for the management of inflammatory conditions such as arthritis.^{41,36}

4. Immune system support: Bitter melon has been traditionally used to support immune function. Studies have shown that bitter melon extracts can enhance the activity of immune cells, such as natural killer (NK) cells and macrophages, which play a crucial role in immune defense. Bitter melon extracts have also exhibited antibacterial and antiviral properties, possibly contributing to their traditional use for infectious diseases.^{42,43}

Bitter melon bioactive compounds and mechanisms of action

Bitter melon contains various bioactive compounds that contribute to its therapeutic effects. Some essential compounds identified in bitter melon include charantin, polypeptide-p, vicine, momordicin, and various flavonoids and phenolic compounds.

Charantin, one of the major bioactive compounds in bitter melon, is believed to contribute to its anti-diabetic properties. It has been found to exhibit hypoglycemic effects by increasing glucose uptake and utilization in peripheral tissues and inhibiting intestinal glucose absorption.⁴¹ Charantin stimulates insulin release from pancreatic beta cells, promoting better glycemic control.⁴⁴

Polypeptide-p is a bioactive compound found in bitter melon that mimics the action of insulin. It reduces blood glucose levels through enhanced glucose uptake by peripheral tissues and suppression of glucose production in the liver.⁴⁵ Polypeptide-p has antioxidant properties and may help protect pancreatic beta cells from oxidative damage.⁴⁵

Vicine, another compound present in bitter melon, has been reported to possess hypoglycemic activity. It may enhance glucose utilization and reduce hepatic glucose production, improving glycemic control.⁴⁵

Momordicin is a type I ribosome-inactivating protein found in bitter melon. It has been shown to have antiviral, antitumor, and immunomodulatory effects.⁴⁵ While its direct impact on diabetes management is not well-studied, its overall health benefits may indirectly contribute to better metabolic health.

Bitter melon also contains various flavonoids and phenolic compounds with antioxidant and anti-inflammatory properties. These compounds may help reduce oxidative stress, inflammation, and insulin resistance, improving insulin sensitivity and glycemic control.⁴⁶

Bitter melon impact on insulin sensitivity and insulin secretion

Studies have explored the impact of bitter melon extracts on insulin sensitivity and secretion. Animal and in vitro studies have shown that bitter melon extracts can improve insulin sensitivity by enhancing glucose uptake in peripheral tissues, such as skeletal muscle and adipose tissue.⁴⁷ These extracts have also been reported to stimulate insulin secretion from pancreatic beta cells, improving glycemic control.⁴⁴

Several clinical studies have investigated the effects of bitter melon on insulin sensitivity and glycemic control in individuals with diabetes. These studies have shown mixed results, with some demonstrating improvements

in insulin sensitivity and glycemic markers while others have reported no significant effects.⁴⁶⁻⁴⁸ It is important to note that the dosages and preparations of bitter melon extracts can vary across studies, which may contribute to the differences in outcomes.

Further research, including well-designed clinical trials, is needed to determine the optimal dosages, preparations, and long-term effects of bitter melon supplementation on insulin sensitivity and secretion in individuals with diabetes.

Previous studies on the anti-diabetic effect of bitter melon

According to research by Mohammady et al.³⁹ on the effect of *Momordica charantia* extract on glucose tolerance and some biochemical parameters in alloxan-induced diabetes, comparing it to the impact of rosiglitazone maleate, an oral hypoglycemic drug, and to suggest the possible mechanisms of its action.³⁹ Rats were divided into 5 groups: normal control, rats received bitter melon, diabetic control, diabetic treated with rosiglitazone (4 mg/kg BW), and the diabetic received *Momordica charantia* (300 mg/kg BW). After 4 weeks, significantly increased insulin release from the pancreas and serum insulin level, increased glucose uptake by rat diaphragm, and decreased intestinal glucose absorption ($p < 0.05$). Bitter melon treatment of diabetic rats resulted in significant hypoglycemic and hypolipidemic effects as compared to rosiglitazone ($p < 0.05$). Anti-diabetic effects of bitter melon may include increasing insulin release and serum insulin, increasing glucose uptake by muscles, decreasing intestinal glucose absorption, and having a hypolipidemic effect.

Potential side effects or adverse reactions of bitter melon

Bitter melon is generally considered safe for consumption when used in moderation. However, there are potential side effects and precautions to consider.

Bitter melon has a naturally bitter taste, which some people may find unpleasant. Excessive bitter melon or its extracts may cause gastrointestinal discomfort, including abdominal pain, diarrhea, or nausea.⁴⁷

Individuals who are pregnant or breastfeeding should exercise caution when consuming bitter melon due to its potential uterine stimulant effects.⁴⁹ It is advisable to consult with a healthcare professional before incorporating bitter melon extracts into the diabetes management regimen. Bitter melon may interact with certain medications, including antidiabetic medicines, leading to hypoglycemia. Therefore, individuals taking drugs for diabetes should monitor their blood glucose levels closely and consult with a healthcare professional before using bitter melon extracts.⁴⁶

Ginger (*Zingiber officinal*)

Ginger (*Zingiber officinale*) is a popular spice and medicinal herb used for centuries in various traditional medicine systems. It is known for its distinct flavor and aroma and is widely used in culinary preparations worldwide. In addition to its culinary uses, ginger has

gained attention for its potential health benefits, including its effects on insulin sensitivity and diabetes management.⁵⁰

Traditional use of ginger

Ginger (*Zingiber officinale*) is a widely used spice and medicinal plant with a long history of traditional use. It has been utilized in various traditional medicine systems, including Ayurveda, Traditional Chinese Medicine, and traditional healing practices in many cultures.⁵¹

1. Digestive aid: Ginger has traditionally alleviated digestive discomfort and promoted digestive health. It is known for its carminative properties, which help relieve symptoms such as bloating, gas, and indigestion.⁵² Ginger has also been used to stimulate appetite and improve digestion.⁵³ It is often consumed as a tea or in meals to support digestive function.

2. Nausea and vomiting: Ginger has a long history of traditional use for reducing nausea and vomiting, including motion sickness, morning sickness during pregnancy, and chemotherapy-induced nausea.⁵⁴ Several studies have reported the antiemetic (anti-nausea) properties of ginger, attributing them to its active compounds, such as gingerols and shogaols.⁵⁵

3. Anti-inflammatory and pain relief: Ginger has been traditionally used for its anti-inflammatory properties and to relieve pain associated with various conditions.⁵⁶ It is believed to inhibit inflammatory pathways and reduce the production of inflammatory mediators.⁵⁷ Traditional use of ginger includes its application topically or consumption as a tea or in food to alleviate pain associated with arthritis, muscle soreness, and menstrual cramps.⁵³

4. Immune support: Ginger has been traditionally used to support the immune system and protect against infections. It is believed to possess antimicrobial properties, including against bacteria and viruses. Traditional use of ginger includes its consumption as a tea or inclusion in meals to promote overall immune health.⁵⁸

Bioactive compounds and mechanisms of action

Ginger contains a variety of bioactive compounds that contribute to its pharmacological properties. Some of the essential compounds found in ginger include gingerols, shogaols, paradols, zingerones, and various flavonoids.⁵⁹

Gingerols are the most abundant bioactive compounds present in fresh ginger. They possess anti-inflammatory, antioxidant, and analgesic properties. Gingerols have been found to inhibit the production of pro-inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing inflammation.⁵⁷ They also scavenge free radicals and reduce oxidative stress.⁶⁰

Shogaols, derived from gingerols during the drying or cooking process, exhibit similar pharmacological activities to gingerols. They possess anti-inflammatory and antioxidant effects and have been suggested to be more potent than gingerols in specific contexts.⁶¹

Paradols are another group of bioactive compounds found in ginger. They possess antioxidant and anti-inflammatory properties and have been shown to

modulate signaling pathways involved in inflammation, such as nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinases (MAPKs).⁶²

Zingerones, derived from gingerols, also exhibit antioxidant, anti-inflammatory, and anti-cancer activities. They have been found to suppress inflammatory mediators and inhibit the growth of cancer cells through mechanisms such as cell cycle arrest and induction of apoptosis.⁶³

Flavonoids in ginger, such as gingerenones and gingerols, contribute to its antioxidant and anti-inflammatory effects. They scavenge free radicals, reduce oxidative stress, and modulate inflammatory pathways, exerting protective effects on various organs and systems.⁶¹

These bioactive compounds in ginger collectively contribute to its beneficial health and disease management effects.

Ginger impact on insulin sensitivity and insulin secretion

Insulin sensitivity refers to the body's ability to respond to insulin and utilize glucose effectively. Impaired insulin sensitivity is a hallmark of conditions like insulin resistance and type 2 diabetes. Ginger extracts have been studied for their potential effects on insulin sensitivity and secretion.

Animal studies have shown promising results regarding the impact of ginger on insulin sensitivity. Ginger supplementation has been found to improve insulin sensitivity by enhancing glucose uptake in peripheral tissues and reducing insulin resistance.^{64,65} These effects may be mediated by the modulation of various molecular pathways involved in glucose and lipid metabolism, such as the insulin signaling pathway and glucose transporter expression.⁶⁵

Regarding insulin secretion, ginger has been reported to have stimulatory effects on pancreatic beta cells, leading to increased insulin release.^{64,65} This may contribute to improved glycemic control and regulation of blood glucose levels.

While animal studies have shown promising results, clinical studies in humans have provided mixed findings. Some human studies have reported improved insulin sensitivity and glycemic control with ginger supplementation, while others have not observed significant effects.⁶⁶⁻⁶⁸ Further research, including well-designed clinical trials, is needed to establish the optimal dosages, treatment durations, and long-term effects of ginger supplementation on insulin-related parameters in individuals with diabetes.^{69,70}

Previous studies on the anti-diabetic effect of ginger

Al-Azhary et al. conducted a study on diabetic cholesterol-fed rats to examine the effects of ginger on blood glucose, lipids, oxidative stress, and early stages of atherogenesis.⁷¹ The rats were divided into control, diabetic cholesterol-fed, and diabetic cholesterol-fed rats were administered ginger (25 mg/kg). Diabetes was induced in both the second and third groups of animals by intraperitoneal injection with one dose of streptozotocin (60 mg/kg). After six weeks, ginger administration led

to a decrease in blood glucose and triglyceride levels. However, it did not fully restore the increase in cholesterol and low-density lipoprotein cholesterol levels. Ginger also reduced malondialdehyde concentration and increased total plasma antioxidant activity. Electron microscopy studies showed that ginger improved the cellular changes in the aortic wall of diabetic cholesterol-fed rats.⁷²

According to a study by Ojewole *et al.*, administering an alcoholic extract of ginger orally at a dosage of 800 mg/kg resulted in a significant reduction in fasting blood sugar levels in streptozotocin (STZ)-diabetic rats.⁷³ The maximum effect was observed after 4 hours, and blood glucose levels were reduced by 24-53%, with doses ranging from 100 mg/kg to 800 mg/kg. Also, a study by Islam and Choi 2008 used a nicotinamide and low-dose STZ-diabetic rat model.⁶⁰ It was observed that oral administration of ginger powder at a dose of 200 mg/kg led to alleviating signs associated with metabolic syndrome. These signs included reductions in blood glucose and serum lipids and increased total antioxidant capacity (TAC).

Potential side effects or adverse reactions of ginger

Ginger is generally considered safe for consumption, and adverse reactions are rare when consumed in moderate amounts. However, some individuals may experience mild gastrointestinal symptoms such as heartburn, bloating, or diarrhea.⁷⁴

Ginger may have antiplatelet and anticoagulant properties, which can affect blood clotting.⁷⁵ Therefore, individuals taking anticoagulant medications or those with bleeding disorders should exercise caution and consult with a healthcare professional before using ginger supplements.⁷⁶ In rare cases, allergic reactions to ginger have been reported. Symptoms may include rash, itching, swelling, or difficulty breathing.⁷⁷

Ginger may interact with certain medications, including antidiabetic medicines, leading to hypoglycemia or potentiation of their effects.⁷⁸

Pregnant women and individuals with gallstones or other gallbladder conditions should also exercise caution and consult with a healthcare professional before using ginger supplements, as ginger may affect gallbladder function or stimulate contractions in pregnant women.⁷⁹

Conclusion

In conclusion, the review underscores the significant potential of local medicinal plants in Nigeria for managing diabetes mellitus. Aloe vera, bitter leaf, bitter lemon, and ginger have shown promising effects in modulating glucose metabolism, enhancing insulin sensitivity, and influencing various physiological parameters associated with diabetes. However, while the findings are encouraging, more rigorous research, including clinical trials, is necessary to validate their efficacy, elucidate underlying mechanisms, and assess long-term safety profiles. Incorporating these traditional remedies into mainstream diabetes management strategies could offer cost-effective and culturally appropriate interventions to alleviate the burden of diabetes in Nigeria and similar regions. Further

collaboration between traditional medicine practitioners, researchers, and healthcare professionals is essential to harness the full potential of local medicinal plants in combating diabetes and improving public health outcomes.

Conflict of interest

The Authors have declared no conflict of interest concerning this work or its publication.

References

- [1] Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, and Yancy WS. Nutrition therapy for adults with diabetes or prediabetes: A consensus report. *Diabetes Care*. 2019; 42(5): 731-54. doi: 10.2337/dci19-0014.
- [2] Gupta RK, Patel AK, Shah N, Chaudhary AK, and Jha UK. A review on medicinal plants with antidiabetic activity. *J Pharmacogn Phytochem*. 2017; 6(6): 2340-5. doi:10.7897/2230-8407.097122
- [3] Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England J Med*. 2011; 345(11): 790-7. doi: 10.1056/NEJMoa010492.
- [4] Piko P, Werissa NA, Fiatal S, Sander J, and Adany R. Impact of Genetic Factors on the Age of Onset for Type 2 Diabetes Mellitus in Addition to the Conventional Risk Factors. *J Pers Med*. 2020; 11(1): 6. doi: 10.3390/jpm11010006.
- [5] Kahn SE, Hull RL, and Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006; 444(7121): 840-6. doi: 10.1038/nature05482.
- [6] Malik VS, Popkin BM, Bray GA, Després JP, and Willett WC. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. 2010; 121(11): 1356-64. doi: 10.1161/CIRCULATIONAHA.109.876185.
- [7] Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*. 2016; 39(11): 2065-79. doi.org/10.2337/dc16-1728
- [8] Vincent AM, Russell JW, Sullivan KA, Backus C, Hayes JM, McLean LL, et al. SOD2 protects neurons from injury in cell culture and animal models of diabetic neuropathy. *Exp Neurol*. 2004; 186(2): 216-27
- [9] Alope C, Egbu CO, Aja PM, Obasi NA, Chukwu J, Akumadu BO, et al. Current advances in the management of diabetes mellitus. *Biomedicine*. 2022; 10(10): 2436. doi.org/10.3390/biomedicine10102436
- [10] Grover JK, Yadav S. Pharmacological actions and potential uses of *Momordica charantia*: A review. *J Ethnopharmacol*. 2004; 93(1): 123-32. doi: 10.1016/j.jep.2004.03.035.
- [11] Surjushe A, Vasani R, and Saple DG. Aloe vera: A short review. *Indian J Dermatol*. 2008; 53(4): 163-6. doi: 10.4103/0019-5154.44785.
- [12] Sánchez M, González-Burgos E, Iglesias I, and Gómez-

- Serranillos MP. Pharmacological update properties of aloe vera and its major active constituents. *Molecules* (Basel, Switzerland). 2020; 25(6): 1324. doi: 10.3390/molecules25061324.
- [13] Paulsen E. Aloe vera gel research review. *J Nat Med*. 2009; 1(1): 1-5.
- [14] Hekmatpou D, Mehrabi F, Rahzani K, and Aminiyan A. The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic review. *Iran J Med Sci*. 2019; 44(1): 1-9. PMCID: PMC6330525. PMID: 30666070
- [15] Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH, and Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study. *Trop Med Int Health*. 1996; 1(4): 505-9. doi: 10.1046/j.1365-3156.1996.d01-91.x.
- [16] Langmead L, Feakins RM, Goldthorpe S, Holt H, Tsironi E, De Silva A, et al. Randomized, double-blind, placebo- controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther*. 2004; 19(7): 739-47. doi: 10.1111/j.1365-2036.2004.01902.x.
- [17] Davis K, Philpott S, Kumar D, and Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. *Int J Clin Pract*. 2006; 60(9): 1080-6. doi: 10.1111/j.1742-1241.2006.00980.x.
- [18] Vogler BK, and Ernst E. Aloe vera: A systematic review of its clinical effectiveness. *Br J Gen Pract*. 1999; 49(447): 823-8. PMID: 10885091, PMCID: PMC1313538
- [19] Yagi A, Kabash A, Okamura N, Haraguchi H, Moustafa SM, Khalifa TI. Antioxidant, free radical scavenging and anti-inflammatory effects of aloesin derivatives in Aloe vera. *Planta Medica*. 2002; 68(11): 957-60. <https://doi.org/10.1055/S-2002-35666/ID/2>
- [20] Dede S, Isirima J, and Akoko S. Antihyperglycemic and histological effect of *Aloe vera* on alloxan-induced diabetes in Wistar rats. *Scholars Int J Integr Med*. 2023; 6: 120-8. doi.org/10.36348/sijtc.2023.v06i08.001
- [21] Arora M, Sarup Y, Tomar R, Singh M, and Kumar P. Amelioration of diabetes-induced diabetic nephropathy by *Aloe vera*: Implication of oxidative stress and hyperlipidemia. *J Diet*. 2018; Suppl16(1): 1-18. <https://doi.org/10.1080/19390211.2018.1499474>
- [22] Boudreau MD, Beland FA, and Nichols JA. Toxicology and carcinogenesis studies of a nondecolorized whole leaf extract of *Aloe barbadensis* Miller (Aloe vera) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Program Tech Rep Ser*. 2013; 577: 1-266. PMID: 24042237
- [23] Ghosh S, and Das S. Quercetin selectively inhibits insulin receptor function in vitro by impairing insulin binding. *Br J Pharmacol*. 2010; 161(2): 424-40. doi: 10.1021/bi00149a041.
- [24] Mosisa Gudeta, B., Melesie Taye, G., Abula, T., & Alemayehu Gadisa, D. Evaluation of anti-diarrheal activity of 80% methanol extracts of vernonia amygdalina delile (asteraceae) leaves in mice. *Journal of Experimental Pharmacology*. 2020; 455-462.
- [25] Boudreau MD, Beland FA, and Nichols JA. Toxicology and carcinogenesis studies of a nondecolorized whole leaf extract of *Aloe barbadensis* Miller (Aloe vera) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Progr Tech Rep Ser*. 2013; 577: 1-266. PMID: 24042237.
- [26] Farombi O, and Owoeye O. Antioxidative and Chemo-preventive Properties of Vernonia amygdalina and Garcinia biflavonoid. *Int J Environ Res Public Health*. 2011; 8: 2533-55. doi: 10.3390/ijerph8062533.
- [27] Igoli J, Ogaji O, Tor-Anyiin T. and Igoli N. Traditional medicine practice amongst the Igde people of Nigeria. Part II. *Afr J Trad CAM*. 2005; 2(2): 134-52. doi:10.4314/ajtcam.v2i2.31112
- [28] Omoregie ES, and Pal A. Antiplasmodial, antioxidant and immunomodulatory activities of ethanol extract of Vernonia amygdalina del. Leaf in Swiss mice. *Avicenna J Phytomed*. 2016; 6(2): 236-47. PMID: 27222837, PMCID: PMC4877969
- [29] Akerele GP, Adedayo C, Oboh, G, Ademolu AO, and Oyeleye SI. Glycemic indices and effect of bitter leaf (*Vernonia amygdalina*) flavored non-alcoholic wheat beer (NAWB) on key carbohydrate metabolizing enzymes in high fat diet fed (HFD)/STZ-induced diabetic Wistar rats. *J Food Biochem*. 2022; 46(12): e14511. 4. doi: 10.1111/jfbc.14511.
- [30] Atangwho II, Yin KB, Umar MI, Ahmad M, and Asmawi MZ. Vernonia amygdalina simultaneously suppresses gluconeogenesis and potentiates glucose oxidation via the pentose phosphate pathway in streptozotocin-induced diabetic rats. *BMC Complementary Altern Med*. 2014; 14: 426. doi: 10.1186/1472-6882-14-426.
- [31] Adedapo AA, Aremu OJ, and Oyagbemi AA. Antioxidant, anti-inflammatory and antinociceptive properties of the acetone leaf extract of vernonia amygdalina in some laboratory animals. *Adv Pharm Bull*. 2014; 4(Suppl 2): 591-8. doi: 10.5681/apb.2014.087.
- [32] Aruoma OI, Colonnato R, Fontana I, Gartlon J, Migliore L, and Koike K. Molecular effects of fermented papaya preparation on oxidative damage, MAP Kinase activation and modulation of the benzo[a]pyrene mediated genotoxicity. *Biofactors*. 2000; 12(1-4): 229-40. doi: 10.1002/biof.5520260205.
- [33] Jaiswal N, Pardhasaradhi PV, and Kuhnert N. Phenolic compounds from Vernonia amygdalina and their antioxidant activities. *Ind Crop Prod*. 2017; 95: 662-7.
- [34] Johnbull O, Igbe I, Obsrisiagbon P, and Onyegbula C. Studies on the effects of Vernonia amygdalina aqueous leaf extract on the biochemical, hematological, and hypoglycemic parameters in diabetic rats: Prerequisite to formulation into pharmaceutical dosage form. *J med Pharm Allied Sci*. 2019; 16.
- [35] Nwaoguikpe R. The effect of extract of bitter leaf (*Vernonia amygdalina*) on blood glucose levels of diabetic rats. *Int J Biol Chem Sci*. 2010; 4(3): 788-96. doi.org/10.4314/ijbcs.v4i3.60500
- [36] Oboh G, Ademiluyi AO, and Akinyemi AJ. Inhibition of α -amylase and α -glucosidase activities by ethanolic extract of Vernonia amygdalina leaf: an in vitro

- assessment. J Taibah Univ Sci. 2016; 10(5): 600-6. doi: 10.1016/S2221-1691(12)60219-6.
- [37] Kim B, Lee HS, Kim HJ, Lee H, Lee IY, Ock S, Kwon S, Kang SS, Choi Y. *Momordica charantia* (bitter melon) efficacy and safety on glucose metabolism in Korean prediabetes participants: a 12-week, randomized clinical study. Food Sci Biotechnol. 2022; 14;32(5):697-704. doi:10.1007/s10068-022-01214-9. PMID: 37009042; PMCID: PMC10050654.
- [38] Duke JA. *Duke's handbook of medicinal plants of Latin America*. CRC Press. 2008
- [39] Mohammady I, Elattar S, Mohamed S, and Ewais M. An evaluation of anti-diabetic and anti-lipidemic properties of *Momordica charantia* (bitter melon) fruit extract in experimentally induced diabetes. J Life Sci. 2012; 9(4): 363-74.
- [40] Jia S, Shen M, Zhang F, Xie J. Recent Advances in *Momordica charantia*: Functional Components and Biological Activities. Int J Mol Sci. 2017; 18(12):2555. doi:10.3390/ijms18122555. PMID: 29182587; PMCID: PMC5751158.
- [41] Joseph B, and Jini D. Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. Asian Pac J Trop Dis. 2013; 3(2): 93-102. doi: 10.1016/S2222-1808(13)60052-3
- [42] Alam MA, Uddin R, Subhan N, Rahman MM, Jain P, and Reza HM. Beneficial role of bitter melon supplementation in obesity and related complications in metabolic syndrome. J Lipid. 2015; Article 496169. doi.org/10.1155/2015/496169.
- [43] Mahwish FS, Nosheen F, Qurat-ul-Ain NB, Afzaal M, Ehsan K, Hussain M, Imran M, and Al JE. Bio-evaluation of alkaloids and saponins from bitter melon: Probing more desirable compounds in treating hyperglycemia and hyperlipidemia. Cogent Food Agri. 2023; 9(1): 1-16. doi:10.1080/23311932.2023.2242634
- [44] Yadav M, Jain S, Tomar R, Prasad GB, and Yadav H. Medicinal and biological potential of pumpkin: an updated review. Nutr Res Rev. 2010; 23(2): 184-90. doi: 10.1017/S0954422410000107.
- [45] Grover JK, Yadav SP, and Vats V. Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol. 2002; 81(1): 81-100. doi: 10.1016/S0378-8741(02)00059-4.
- [46] Bhattacharya S, Muhammad N, Steele R, Kornbluth J, and Ray RB. Bitter Melon Enhances Natural Killer-Mediated Toxicity against Head and Neck Cancer Cells. Cancer Prev Res (Philadelphia, Pa.). 2017; 10(6): 337-44. doi: 10.1158/1940-6207.CAPR-17-0046
- [47] Sur S, and Ray RB. Diverse roles of bitter melon (*Momordica charantia*) in prevention of oral cancer. J Cancer Metastasis Treat. 2021; 7: 12. https://doi.org/10.20517/2394-4722.2020.124
- [48] Leatherdale BA, Panesar RK, Singh G, and Atkins TW. Improvement in glucose tolerance due to *Momordica charantia* (karela). Br Med J (Clin Res Ed). 1981; 282(6279): 1823-4. doi:10.1136/bmj.282.6279.1823.
- [49] Ahmed I, Adeghate E, Cumming E, and Sharma AK. Beneficial effects and mechanisms of action of *Momordica charantia* juice in the treatment of streptozotocin-induced diabetes mellitus in rat. Mol Cell Biochem. 2012; 368(1-2): 59-73. doi: 10.1023/b:mcbi.0000028738.95518.90.
- [50] Basch E, Gabardi S, and Ulbricht C. Bitter melon (*Momordica charantia*): A review of efficacy and safety. Am J Health Syst Pharm. 2003; 60(4): 356-9. doi: 10.1093/ajhp/60.4.356.
- [51] Fuangchan A, Sonthisombat P, Seubnukarn T, Chanouan R, Chotchaisuwat P, and Sirigulsatien V. Hypoglycemic effect of bitter melon compared with metformin in newly diagnosed type 2 diabetes patients. J Ethnopharmacol. 2011; 134(2): 422-8. doi: 10.1016/j.jep.2010.12.045.
- [52] Oishi Y, Sakamoto T, Udagawa H, Taniguchi H, and Kobayashi-Hattori K. *Momordica charantia* L. improves insulin resistance and disordered lipid metabolism in a high-fructose diet-induced NAFLD mouse model. Arch Biochem Biophys. 2019; 662: 169-78. doi: 10.3389/fphar.2021.770652
- [53] Ooi CP, Yassin Z, Hamid TA, & Momtaz YA. *Momordica charantia* for type 2 diabetes mellitus. Cochrane Database Sys Rev. 2013; (8): CD007845. https://doi.org/10.1002/14651858.CD007845.pub3
- [54] Grzanna R., Lindmark L., & Frondoza, C. G. Ginger--an herbal medicinal product with broad anti-inflammatory actions. *Journal of medicinal food*. 2005; 8(2), 125–132. https://doi.org/10.1089/jmf.2005.8.125
- [55] Alam MA, Uddin R, Subhan N, Rahman MM, Jain P, and Reza HM. Beneficial role of bitter melon supplementation in obesity and related complications in metabolic syndrome. J Lipid. 2015; Article 496169. https://doi.org/10.1155/2015/496169.
- [56] Ali BH, Blunden G, Tanira MO, and Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. Food Chem Toxicol. 2008; 46(2): 409–20. doi: 10.1016/j.fct.2007.09.085.
- [57] Black CD, Herring MP, Hurley DJ, and O'Connor PJ. Ginger (*Zingiber officinale*) reduces muscle pain caused by eccentric exercise. J Pain. 2010; 11(9): 894-903. doi: 10.1016/j.jpain.2009.12.013.
- [58] Ernst E, and Pittler MH. Efficacy of ginger for nausea and vomiting: A systematic review of randomized clinical trials. Br J Anaesth. 2000; 84(3): 367-71. doi: 10.1093/oxfordjournals.bja.a013442.
- [59] Viljoen E, Visser J, Koen N, and Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014; 13: Article 20. doi.org/10.1186/1475-2891-13-20
- [60] Islam MS, and Choi H. Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. J Med Food. 2008; 11(1): 152-9. doi.org/10.1089/jmf.2007.601.3r
- [61] Grzanna R., Lindmark L., & Frondoza, C. G. Ginger--

- an herbal medicinal product with broad anti-inflammatory actions. *Journal of medicinal food*. 2005; 8(2), 125–132. <https://doi.org/10.1089/jmf.2005.8.125>
- [62] Rahmani AH, Shabrimi FM, and Aly, SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. *Int J Physiol Pathophysiol Pharmacol*. 2014; 6(2): 125-36. PMID: PMC4106649 PMID: 25057339
- [63] Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, and Li HB. Bioactive compounds and bioactivities of ginger (*Zingiber officinale* Roscoe). *Foods* (Basel, Switzerland). 2019;8(6):185.doi:10.3390/foods8060185.
- [64] Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L, and Mofid MR. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: Review of current evidence. *Int J Prev Med*. 2013; 4(Suppl 1): S36-S42. PMID: 23717767, PMCID: PMC3665023
- [65] Bode AM, and Dong Z. The amazing and mighty ginger. In *Herbal Medicine: Biomolecular and Clinical Aspects* (2nd ed.). Boca Raton (FL): CRC Press/Taylor & Francis.2011
- [66] Kundu JK, Na HK, and Surh YJ. Ginger-derived phenolic substances with cancer preventive and therapeutic potential. *Forum of Nutr*. 2009; 61: 182-92. doi: 10.1159/000212750.
- [67] Gan FF, Nagle AA, and Ang X. Ginger lowers blood pressure through blockade of voltage-dependent calcium channels. *J Cardiovasc Pharmacol*. 2011; 57(4): 468-73. doi: 10.1097/00005344-200501000-00013
- [68] Akhane SP, Vishwakarma SL, Goyal RK, and Chauhan DK. Pharmacological evaluation of *Cucumis sativus* Linn. for central nervous system depressant activity. *J Basic Clin Physiol Pharmacol*. 2014; 25(3): 335-42. doi:10.3126/jucms.v11i03.61478
- [69] Arablou T, Aryaeian N, Valizadeh M, Sharifi F, Hosseini A, and Djalali M. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. *Int J Food Sci Nutr*. 2014; 65(4): 515-20. doi: 10.3109/09637486.2014.880671
- [70] Daily JW, Zhang X, Kim DS, and Park S. Efficacy of ginger for treating type 2 diabetes: A systematic review and meta-analysis of randomized clinical trials. *J Ethn Foods*. 2015; 2(1): 36-43. doi:10.1016/j.jef.2015.02.007
- [71] Al-Azhary D. Ginger enhances antioxidant activity and attenuates atherogenesis in diabetic cholesterol-fed rats. *Aust J Basic Appl Sci*. 2010; 5(10): 1357-64.
- [72] American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2021; 44(Supplement_1): S15-S33.
- [73] Ojewole JA. Analgesic, anti-inflammatory, and hypoglycemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes (*Zingiberaceae*) in mice and rats. *Phytother Res: PTR*. 2006; 20(9): 764-72. doi.org/10.1002/ptr.1924
- [74] Langner E, Greifenberg S, and Gruenwald J. Ginger: history and use. *Adv Ther*. 1998; 15(1): 25-44. PMID: 10178636.
- [75] Mozaffari-Khosravi H, Talaei B, Jalali BA, Najarzadeh A, and Mozayan MR. The effect of ginger powder supplementation on insulin resistance and glycemic indices in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Complement Ther Med*. 2014; 22(1): 9-16. doi: 10.1016/j.ctim.2013.12.017.
- [76] White B. Ginger: An overview. *Am Fam Physician*. 2007; 75(11): 1689-91. PMID: 17575660
- [77] Dumanoglu B, Alpagat G, Poyraz M, Alan YS, and Baccioglu A. Anaphylaxis After Consumption of Guar Gum-Containing Food: A Report of Two Cases. *Cureus*. 2022; 14(8): e28022. doi: 10.7759/cureus.28022
- [78] Khandouzi N, Shidfar F, Rajab A, Rahideh T, Hosseini P, and Mir Taheri M. The effects of ginger on fasting blood sugar, hemoglobin a1c, apolipoprotein B, apolipoprotein a-I and malondialdehyde in type 2 diabetic patients. *Iran J Pharm Res: IJPR*. 2015; 14(1): 131-40. PMID: 25561919, PMCID: PMC4277626
- [79] Chuah SK, Wu KL, Tai WC, and Changchien CS. The effects of ginger on gallbladder motility in healthy male humans. *J Neurogastroenterol Motil*. 2011; 17(4): 411-5. doi: 10.5056/jnm.2011.17.4.411.

Comparison of the effectiveness of blacklight blue lamp and wood lamp in the screening of tinea capitis

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ABSTRACT

Background: Tinea capitis is a common fungal infection of the scalp in children. Most cases are caused by *Microsporum canis* or *Trichophyton mentagrophyte*. Wood lamps screen for tinea capitis by detecting green-yellow fluorescence produced by tryptophan metabolites. Because wood lamps are expensive and replacement parts are difficult to find during maintenance, we have developed a blacklight blue lamp device with a similar wavelength that is cheaper than wood lamps.

Objective: To evaluate the BLB lamp device for screening tinea capitis by determining the sensitivity, specificity, and accuracy compared to fungus culture (gold standard).

Materials and methods: One hundred seventy-five patients with suspected tinea capitis were tested using KOH examination, fungal culture, a Wood lamp, and a blacklight blue lamp device. The research data obtained will be used to analyze the sensitivity, specificity, and accuracy of the blacklight blue lamp device by comparing it using various methods.

Results: The analysis assessed the sensitivity, specificity, and accuracy of the blacklight blue lamp device, Wood lamp, and KOH preparation when comparing fungal culture as the standard method for diagnosing tinea capitis. The sensitivity was 99.39%, 100%, and 100%, specificity was 100%, 90.91%, and 100%, and accuracy was 99.43%, 99.43%, and 100%, respectively. The p-value for the three methods' differences was 0.723 for sensitivity, 0.735 for specificity, and 0.676 for accuracy. These results show that the differences between the two methods' sensitivity, specificity, and accuracy were not statistically significant.

Conclusion: The blacklight blue lamp device effectively screened tinea capitis with a sensitivity, specificity, and accuracy that were not significantly different from the wood lamp. It may be an inexpensive tool used as a substitute in the health service system.

Introduction

Tinea capitis is most observed in children between 3 and 14 years old.¹ The fungistatic effect of fatty acids in sebum may help to explain the sharp decrease in incidence after puberty. The overall prevalence of the carrier state is approximately 4% in the United States, with a peak prevalence of roughly 13% in girls of sub-Saharan African American descent. The fungistatic effect of fatty acids in sebum may help to decrease incidence after puberty.²

The Southern Regional Hospital of Tropical Dermatology in Trang Province reports that, on average, 24,873 individuals are seen annually, with 227 having tinea capitis on their scalps.³ Therefore, fungal-related skin diseases are common in tropical regions, particularly

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in southern Thailand. At the hospital in the study, dermatologists request laboratory tests for fungus 2,551 times a year on average using the KOH technique for diagnosis and treatment and 363 times a year on average for the kind of fungal infection to be identified using fungal culture on agar, which is the gold standard.

Alternatively, fungi from the *Microsporum* group may be made to glow green-blue due to the chemical pteridine. This approach has the advantage of speeding up the identification of the condition. Wood light is a piece of equipment that the hospital uses 107 times a year on average.⁴ This apparatus aids in diagnosing skin conditions in patients and facilitates the appropriate collection of illness samples. The UVA bulb for the Wood lamp requires replacement after being used for more than 20 years due to deterioration. However, because new bulbs are either too costly or have been discontinued, it is not feasible to replace them.

However, there are currently affordable blacklight blue bulbs on the market. Both bulbs produce bright purple light with the same maximum wavelength of 365 nm. The glass light bulb, which is blue-purple, has a visible light range of 365 nm. It does not appear blue or black but filters off visible blue light. Wood lamp generates ultraviolet light using a glass filter of 9% nickel oxide and barium silicate, with a wavelength of 365 nanometers (320-400 nanometers, or UVA).^{5,6} The wood lamp and blacklight blue lamp device have been compared in previous R2R (routine to research) investigations for differential diagnosis of tinea versicolor and erythrasma. The results showed that the lamp eliminated other wavelengths of light, leaving only blue-white light. The study's findings revealed that the two approaches' respective sensitivity, specificity, and accuracy were 82.05, 97.62, and 90.12 percent. In this example, the blacklight blue lamp device and the wood lamp produced the same diagnostic results.⁷⁻¹⁰ Thus, a machine was conceived to substitute the wood lamp with the blacklight blue lamp device. Furthermore, the blacklight blue device can be linked to a computer or smartphone and can capture still photographs while observing the lesion or from the sample, such as skin or hair. The blue-green hue of pteridine in the diseased region may be seen by shining the blacklight blue lamp device directly at the lesion in tinea capitis infected with *Microsporum canis*.¹¹

At the time of this study, a comparison of the blacklight blue lamp device and wood lamp does not appear in the research on tinea capitis screening in humans. Since blacklight blue can be used to diagnose or screen for tinea capitis, it would no doubt be beneficial for treating the condition and can be practically implemented in the healthcare system. For this reason, the research team decided to examine the efficacy of the blacklight blue lamp device in screening for tinea capitis by considering both analytical sensitivity and specificity.

Materials and methods

Study population

The study focused on patients suspected of having

tinea capitis and was conducted at the Southern Regional Hospital of Tropical Dermatology in Trang Province, Thailand, from October 2022 to September 2024. Participants were eligible if they were aged 3 to 15 years, attended their first consultation at the hospital, had a confirmed diagnosis of tinea capitis, provided informed consent, and demonstrated proficiency in reading, writing, speaking, and understanding Thai. Patients were excluded if they had used topical treatments, oral antifungal medications, or antifungal shampoos for tinea capitis within 60 days before they visited the physician.

Collection

Data were obtained from 175 people with confirmed or suspected tinea capitis at Southern Regional Hospital of Tropical Dermatology, Trang Province, Thailand. Three separate parts made up the questionnaire used to gather data for this study: Part 1 consists of general personal data such as age, gender, occupation, history of using antifungal medications, and chronic disease; Part 2 consists of skin disease diagnosis, including clinical characteristics, location, and diagnosis; and Part 3 consists of laboratory examination with data collection based on laboratory test results and skin disease diagnosis. Utilizing Diagnostic Test statistics, the data results were examined to determine the sensitivity, specificity, and accuracy of the wood lamp, blacklight blue lamp device, and KOH preparation test in comparison to fungal culture, the gold standard for diagnosing tinea capitis.

The following is the research protocol: Using a wood Lamp and blacklight blue lamp device, the dermatologist confirmed the diagnosis of suspected tinea capitis and checked for fluorescence in the lesion.

The sample was taken for the types of specimens using a skin or scalp scrape in the same area as the fluorescence observation. The fungus was grown on Sabouraud dextrose agar containing chloramphenicol and cycloheximide, and the causative fungal species was identified within 28 days. Afterward, enough specimens were collected by dividing the fresh specimens into 10-30% potassium hydroxide (KOH) solution for microscopic examination. A preliminary exam examined the fluorescence from a wood lamp and a blacklight blue lamp device. The results were presented to the doctor for treatment, along with the location of the lesion and its fluorescent hue. The laboratory staff were provided a consent form and invited the patients to participate in the experiment. A dermatologist diagnosed the individuals with fungus.

Screening using the wood lamp and blacklight blue (BLB) lamp device

The screening process utilized the wood and blacklight blue (BLB) lamps. The wood lamp, specifically the UVGL-58 Handheld UV Lamp /P/2 95-0007-06, was employed for ultraviolet examination. The BLB lamp device, developed and patented by the Southern Regional Hospital of Tropical Dermatology in Trang Province (Patent No. 1903002609), was also utilized, as illustrated in Figure 1.

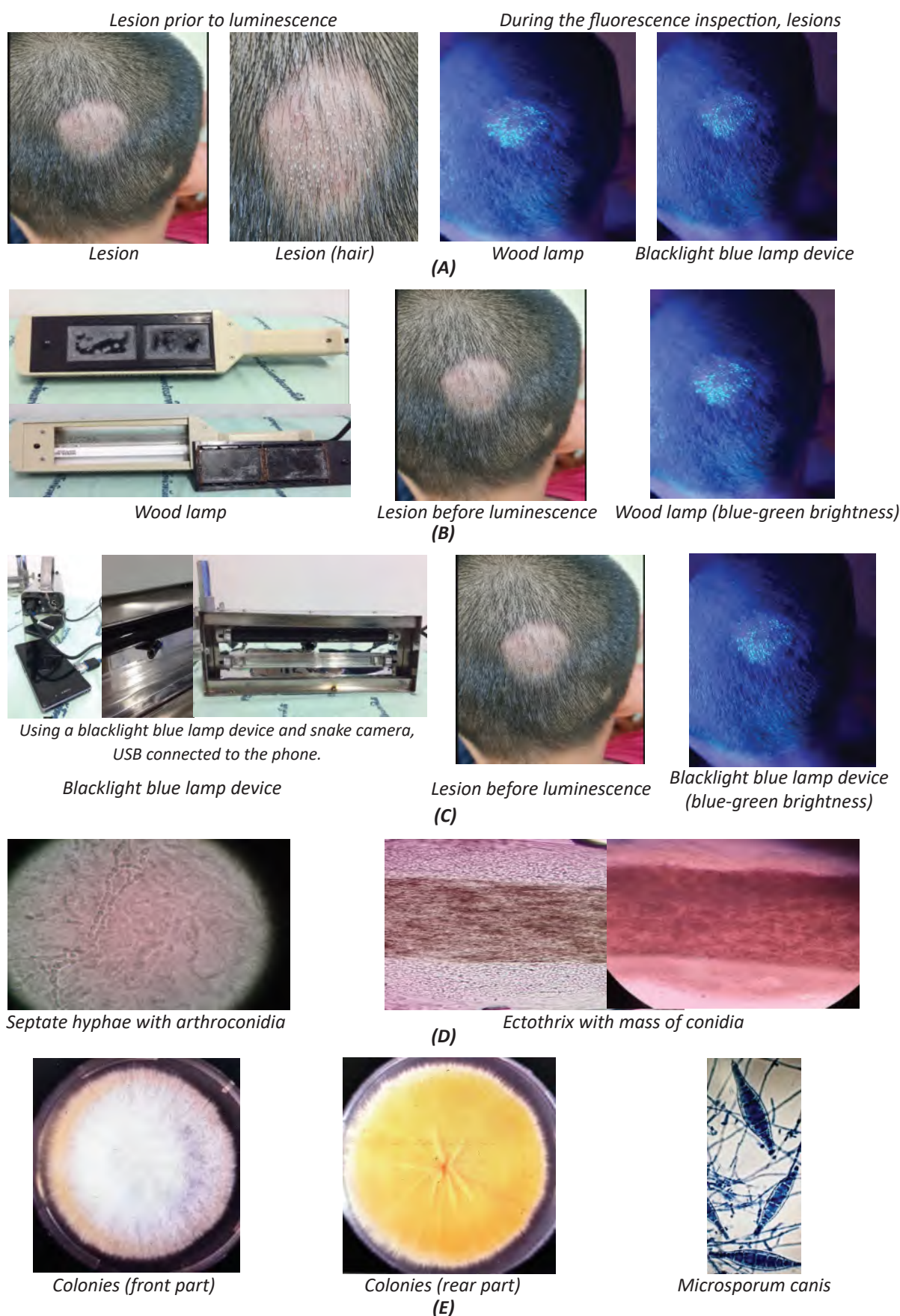


Figure 1. Investigation on fungal culture, blacklight blue lamp device, wood lamp, and KOH preparation for diagnosing tinea capitis. **A:** a comparison of lesions observed before fluorescence and after fluorescence using a wood lamp and a blacklight blue lamp device, **B:** lesions observed before and after fluorescence using a wood lamp, **C:** lesions observed before and after fluorescence using a blacklight blue lamp, **D:** KOH Preparation, **E:** a cultured fungus (gold standard).

Laboratory examination

The fungus was grown on Sabouraud dextrose agar containing chloramphenicol and cycloheximide, and the causative fungal species was identified within 28 days. Afterward, enough specimens were collected by dividing the fresh specimens into 10-30% potassium hydroxide (KOH) solution for microscopic examination. A preliminary exam examined the fluorescence from a wood lamp and a blacklight blue lamp device by laboratory staff trained in the result fluorescence. The results were presented to the doctor for treatment, along with the location of the lesion and its fluorescent hue. The laboratory staff were provided a consent form and invited the patients to participate in the experiment. A dermatologist diagnosed the individuals with fungus.

Statistical analysis

Data analysis was conducted using statistical software and diagnostic test statistics. Categorical data are presented by comparing the blacklight blue lamp device, wood lamp, and KOH preparation of fungal culture as the gold standard for diagnosing tinea capitis to reveal these methods' sensitivity, specificity, and accuracy. The formula diagnostic test statistics calculated the sample size using the n4Studies application,¹²⁻¹⁵ with Se of 0.9, 1-Se of 1-0.9, d^2 of 0.1², and proportion (p) of 0.2. The sample size calculated from the formula was 175. The sensitivity, specificity, and accuracy of the blacklight blue lamp device, wood lamp, and KOH preparation tests were

compared to fungal culture using Pearson's chi-squared test for statistical analyses.

Ethical approval

The complete study was conducted according to the Declaration of Helsinki and approved by the Institute of Dermatology, Bangkok, Thailand Human Ethics Committee (approval number: IRB/IEC 019/2564).

Results

Data on general information and skin disorder diagnosis were used to classify the number and percentage of responders. As shown in Table 1, a total of 175 volunteers participated in the study, of which 114 were male (65.14%) and 61 were female (34.86%). There were 133 (76.00%) children aged 3-9 years and 24 (24.00%) children aged 10 to 15 years, respectively, with a mean age of 8.85 years (SD=3.77). Of the participants, 164 individuals, or 93.71 percent, had no underlying disorders, whereas 11 individuals, or 6.29 percent, did. Tinea capitis affected 175 persons, or 100% of the sample. The head and hair affected 165 individuals, or 94.29 percent of the sample, while the head only affected 4 people, or 2.29 percent, followed by the hair with 6 people, or 3.43%.

Grey patches on the scalp were the most prevalent clinical symptoms, affecting 120 patients or 68.57 percent. These were followed by partial hair loss in 51 patients, 29.14 percent, and diffuse pustular in 4 patients, or 2.29 percent.

Table 1. Data on general information and skin disorder diagnosis were used to classify the number and percentage of responders. (N=175).

Data	Number (N=175)	Percentage
Gender		
Male	114	65.14
Female	61	34.86
Age (years) (Mean=8.85, SD=3.77)		
Pre-existing long-term medical conditions		
No underlying disease	164	93.71
Underlying disease	11	6.29
Provisional diagnosis		
Tinea capitis	175	100
Location		
Scalp	4	2.29
Hairs	6	3.43
Scalp and hairs	165	94.29
Clinical manifestation		
Diffuse pustular	4	2.29
Partial hair loss	51	29.14
Grey patches	120	68.57

Table 2 shows the blacklight blue lamp device analytical findings for sensitivity, specificity, and accuracy compared to a cultured fungus, using the gold standard for determining tinea capitis diagnosis. By screening 175 patients with a blacklight blue lamp device light examination and 175 samples of cultured fungus, it was

discovered that 175 individuals had been diagnosed with tinea capitis. It was found that A total of 164 True Positive samples, or 99.39 percent, were screened using a blacklight blue lamp device to search for fluorescence. The lesion region had a blue-green fluorescence, indicating the pathogen entering the hair.

Table 2. Blacklight blue lamp device analytical findings for sensitivity, specificity, and accuracy compared to a cultured fungus.

Result	Culture fungus (gold standard)	N	%	Indication
Blacklight blue lamp device				
Fluorescent detection (+)	Positive	164	99.39	True positive
	Negative	1	0.61	False positive
No fluorescent detection (-)	Positive	0	0	False negative
	Negative	10	100	True negative
Total results		175		
Sensitivity			99.39	
Specificity			100	
Accuracy			99.43	

Pteridine is the luminous material (pyrimidine-4,5, 2,3-pyrazine). The colonies' smooth surface, like silk or cat hair, is a culture characteristic with a possible groove in the middle of the colony where the yellow edges meet. Under a microscope, the yellow colonies beneath the microconidia seem to be solitary, oval cells that are sparsely protruding from the edges of the fungal stalk. Macroconidia are large, like shuttles, with solid walls, spines, and a pointy tip that curves. *Microsporum canis* is present within, where 6-15 cells develop from the peduncle. The result of fungal culture was positive in about 165 patients with the morphology of colony and microscopic identification that

were shown *Microsporum canis* all 165 colonies as shown in Figure 1, a cultured fungus (gold standard) (E).

Ten true negative samples, or 100 percent, revealed that neither the fungal culture nor the screening using the blacklight blue lamp device's fluorescence revealed any fungal growth in the lesion region.

Table 3 shows the study's findings of the wood lamp's sensitivity, specificity, and accuracy compared to the cultured fungus (gold standard) technique. It shows that 175 patients were diagnosed with the condition, 175 underwent a light examination, and 175 underwent fungal culture.

Table 3. Wood lamp analytical findings for sensitivity, specificity, and accuracy compared to a cultured fungus.

Result	Culture fungus (gold standard)	N	%	Indication
Wood lamp				
Fluorescent detection (+)	Positive	164	100	True positive
	Negative	0	0	False positive
No fluorescent detection (-)	Positive	1	9.09	False negative
	Negative	10	90.91	True negative
Total results		175		
Sensitivity			100	
Specificity			90.91	
Accuracy			99.43	

True positive results of 164 samples, or 100% (from fungal culture is *M. canis*), revealed that the fungal culture had the appearance of a colony with a smooth surface like silk or cat's fur, the yellow edge possibly having a groove at the center of the colony, and the screening by looking at the wood lamp fluorescence in the lesion area showed a blue-green fluorescence of pteridine in the pathological area. Under a microscope, the yellow colony

shows large macroconidia resembling shuttles, thick walls and thorns, a curved pointed tip, and 6-15 cells growing from the peduncle, identified as *Microsporum canis*. The microconidia are single oval cells that grow out from the side of the fungal stalk in small numbers.

Ten samples presented the true negative result. It revealed that no fungus (90.91% of the total) was discovered in the fungal culture and that no fluorescence

was detected in the lesion region using the wood lamp fluorescence screening.

Table 4 presents the findings of examining the KOH Preparation test's sensitivity, specificity, and accuracy

compared to the culture technique, considered the gold standard. The analysis reveals that 175 patients were diagnosed with the condition, 175 underwent the KOH Preparation test, and 175 underwent culture.

Table 4. Results of comparing the KOH preparation test with a culture of fungus in terms of sensitivity, specificity, and accuracy.

Result	Culture fungus (gold standard)	N	%
KOH preparation			
	Positive	165	94.29
	Negative	10	5.71
Total results		175	
Sensitivity			100
Specificity			100
Accuracy			100

Note: The culture fungus had to be compared with the 95% confidence interval, CI.

The KOH preparation test, as shown in Figure 1, indicated ectothrix with a mass of conidia and septate hyphae with arthroconidia, and ectothrix with a mass of conidia and culture showed growth of *Microsporum canis*, according to true positive findings of 165 samples. Furthermore, the true negative findings of ten samples demonstrated that neither fungal growth nor the KOH Preparation test could identify the fungus.

The data was analyzed using diagnostic test statistics, and the findings show that the data had 100% accuracy, 100% specificity, and 100% sensitivity.

When compared to fungal culture, the gold standard for diagnosing tinea capitis, Table 5 shows sensitivity, specificity, and accuracy analysis of the blacklight blue lamp device, wood lamp, and KOH preparation test was 99.39%, 100%, and 100% for sensitivity, 100%, 90.91%, and 100% for specificity, and 94.43%, 100%, and 99.43% for accuracy, respectively. A comparison of the three methods revealed the differences in sensitivity values and no statistically significant differences in sensitivity, specificity, or accuracy; the *p* value was 0.723, the methods' specificity was 0.735, and their accuracy was 0.676.

Table 5 The sensitivity, specificity, and accuracy analysis of the blacklight blue lamp device, wood lamp, and KOH preparation tests compared with the fungal culture.

Test	%		
	Sensitivity	Specificity	Accuracy
Blacklight blue lamp device	99.39	100	99.43
Lamp	100	90.91	99.43
KOH Preparation	100	100	100
<i>p</i> -value	0.723	0.735	0.676

Note: the cultured fungus had to be compared with the *p*-value.

Diagnostic Test statistics were used to analyze the data, and the findings showed that the accuracy, sensitivity, and specificity were, respectively, 99.43 percent, 100 percent, and 99.39 percent.

Under a microscope, microconidia are single, oval cells that grow from the side of the fungal stalk and are few. Macroconidia are large, resembling a shuttle, with a pointed and curved tip, thick wall, and thorns. Inside are 6-15 cells growing from the peduncle, confirmed to be *Microsporum canis*. Tinea capitis of the scalp, wood lamp, and blacklight blue lamp device show a blue-green color. Lastly, the KOH preparation test reveals septate hyphae with arthroconidia or ectothrix with a mass of conidia.

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few. Macroconidia are large, resembling a shuttle, with a pointed and curved tip, thick wall, and thorns. Inside are 6-15 cells growing from the peduncle, confirmed to be *Microsporum canis*. Tinea capitis of the scalp, wood lamp, and blacklight blue lamp device show a blue-green color. Lastly, the KOH preparation test reveals septate hyphae with arthroconidia or ectothrix with a mass of conidia.

Discussion

Microsporum canis infection is the cause of tinea capitis. A long-used instrument known as a Wood light was formerly present in the hospital unit, but its degradation impacted the service. As a result, patients and physicians who made laboratory diagnoses did not receive the appropriate care. Market analysis showed that blacklight

blue lamps are less costly, have a visible light range of 365 nanometers, have the same maximum wavelength (365 nm), and have light purple characteristics. The wood lamp, on the other hand, is a device that produces ultraviolet light with a wavelength of 365 nanometers (320-400 nanometers, or UVA) by blocking out other wavelengths and leaving only blue-white light behind. The filter glass is made of barium silicate, and 9% nickel oxide.^{5,6,11} Blacklight blue's look is comparable to a wood desktop lamp and needs to be plugged in. The lamp has a switch for three modes: light purple, bright blue, and adjustable blacklight blue.

In this study, 175 individuals with a history of tinea capitis were tested for KOH preparation, and 175 samples of fungal cultures were collected. Ten of the samples were actual negatives, and 165 were true positives. One sample had a false positive rate of 00.61%. It was discovered that the fluorescence of contaminants such as cotton swabs, gauze, flour, or the use of certain medications before visiting a doctor could be the cause of a false positive in a blacklight blue machine screening. As for fungal culture, it could have been caused by microorganisms present during sample collection, laboratory examinations, contamination of culture media, local organisms in the sample, or even pathogenic fungi from other samples examined in the lab.

False Negative is not detected, although the blacklight blue lamp device can detect it. It might be brought on by using ointments on the lesion before visiting a physician or by reducing microorganisms because of treatment. The fungal culture could be the consequence of the patient receiving antifungal medication, where the drug buildup in the hair is high enough to prevent the growth of microbes on the culture medium, or it could come from the scalp and hair samples used for testing that were taken from the ends of the hair that have dead fungi or are unable to multiply. While incidents are rare, false positive findings might occur using wood lamp screening. They might be brought on by using ointments on the lesion before visiting a physician or by the treatment-induced reduction of organisms. The fungal culture might be obtained from the tested scalp and hair samples, from hair ends that contain inactive or dead fungi, or from patients who are receiving antifungal medication and have enough drug build-up in their hair to prevent the organism from growing on the culture medium.

The false negative findings (one sample, 9.09%) suggest that wood lamp screening might have been ointments applied to the lesion before consultation with a physician or a reduction in the number of microorganisms because of therapy. The fungal culture could have originated from the scalp and hair samples used in the examination, taken from hair ends containing dead fungi or incapable of increasing, or from patients whose hair had a high enough concentration of antifungal medication to prevent the growth of microorganisms on the culture medium.

In the case of the KOH preparation test and fungal culture, the wood lamp and blacklight blue lamp devices both aid in properly collecting specimens in the right

location, complying with the guidelines, and enough. Nevertheless, the KOH preparation method may yield false negative results, which could arise from the fact that the hair and scalp samples used in the test were taken from hair ends that contained dead fungi or were unable to multiply or from patients whose drug accumulation was high enough to prevent the fungi on the culture medium from growing. The data was assessed using diagnostic test statistics with a 95% CI.¹⁶⁻¹⁹ The results showed 100% accuracy, 100% specificity, and 100% sensitivity. While KOH preparation has a high sensitivity for fungal detection in samples, it cannot identify or categorize the kind of fungal species present in the samples.¹⁷ Tomotaka Sato *et al.* found that the wood lamp is helpful for the diagnosis of onychomycosis and for monitoring the course of treatment of the disease.²⁰ It is a simple and quick method for looking at the pathological characteristics of the lesion margin and the destruction of the nail caused by fungus. On the other hand, the blacklight blue lamp device is an easy-to-use, rapid-acting instrument consistent with the study results. The tool checks for skin conditions in doctor's examining rooms, including erythrasma, tinea capitis, and tinea versicolor. The light blue lamp device was developed at a cost of under 5,000 Baht by the Southern Regional Hospital of Tropical Dermatology Trang Province. Nevertheless, the wood Lamp costs under 20,000 Baht.

This developed device represented various features during the medical procedure with the sample or lesions, e.g., photo recording, simulating imaging, and connecting to computer or mobile devices. This supports physicians in identifying illnesses quickly, accurately, and efficiently, enhancing the quality of life for those who receive services.

Limitation

Using a wood lamp or blacklight blue lamp device alone might not be enough for a precise diagnosis. It should be combined with other laboratory tests like direct examination or culture to confirm the diagnosis. Both tools are useful for preliminary screening; however, each has limitations: 1) Since other chemicals may be responsible for the luminous material, the type of fungus causing the sickness cannot be recognized, 2) Research in other communities, and 3) Examine the outcomes of therapy fluorescence and other populations.

Conclusion

Using a comparison of fungal culture, the gold standard for diagnosing tinea capitis, the sensitivity, specificity, and accuracy analysis of the blacklight blue lamp device, wood lamp, and KOH preparation test was assessed. It is practical, easy to use, and time-saving for medical professionals in diagnosing and treating patients. A wood or blacklight blue lamp device alone may not diagnose definitively. For confirmation, it is recommended to combine it with other laboratory techniques, such as direct examination or culture testing.

Conflict of interest

None declared.

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References

- [1] Shy R. Tinea corporis and tinea capitis. *Pediatr Rev.* 2007; 28(5): 164-74. doi:10.1542/pir.28-5-164.
- [2] Lahiri, Koushik; Dhar, Subhra1; Saha, Abhijit2; Bashir, Safia3. An Unusual Case of Tinea Capitis Presented as Erythematous, Hyperkeratotic, Scaly Plaque with Alopecia. *Indian Dermatol Online J.* 2024; 15(5): 885-6. doi: 10.4103/idoj.idoj_744_23
- [3] Southern Regional Hospital of Tropical Dermatology-Trang Province. Patient services Data (2019-2021) [Intranet]. Trang, Southern Regional Hospital of Tropical Dermatology-Trang Province; 2021. [cited 2021 jun 15]. Available from: <https://public.tableau.com/app/profile/niti.pandam/viz/DashboardSkin-Trang/Dashboard>.
- [4] Southern Regional Hospital of Tropical Dermatology-Trang Province. Over the previous three years, the number of laboratory analysis items (2019-2021) [Intranet]. [cited 2021 jan 2]. Available from: <https://public.tableau.com/app/profile/niti.pandam/viz/DashboardSkinTrang/Dashboard>
- [5] Insect-O-Cutor. Black Light Insect Attraction Lamps. 2006 [Internet] [updated 2021 May 7; cited 2021 Jun 15]. Available from: <https://www.insect-o-cutor.com/insectolamps.shtml>.
- [6] de Oliveira, D.M., Cavalcante, R.P., da Silva, L.d. *et al.* Identification of intermediates, acute toxicity removal, and kinetics investigation to the Ametryn treatment by direct photolysis (UV254), UV_{254}/H_2O_2 , Fenton, and photo-Fenton processes. *Environ Sci Pollut Res.* 2019; 26: 4348-66 (2019). doi.org/10.1007/s11356-018-1342-6.
- [7] Sripet, B., Phaokeaw C., K., Khaonim, K., Wisessombat, S. Wood Lamp in Differential Diagnosis of Tinea Versicolor, Tinea Capitis, and Erythrasma: A Comparative Study of Ultraviolet Light and Blacklight Blue Lamp. *J Health Sci Thai.* 2023; 32 (4): 692-701. (in Thai) doi: ISSN: 3027-740X.
- [8] Trisirichote, A. Pediatric Tinea Capitis. *Thai Pediatric J.* 2010; 17(1): 26-30. (in Thai). ISBN: 1513-6264.
- [9] Kullavanijaya, P. Pisarnbutr, P. *Dermatology; Superficial fungal.* 1st Ed. Holistic Publishing CO., LTD., 2012: 35-47.
- [10] DeTar LG, Dubrovsky V, Scarlett JM. Descriptive epidemiology and test characteristics of cats diagnosed with *Microsporum canis* dermatophytosis in a North-western US animal shelter. *J Feline Med Surg.* 2019; 21(12): 1198-205. doi:10.1177/1098612X19825519.
- [11] Luplerdlop N, and Suwanmanee S. Dermatophytosis: From bench to bedside. *J Trop Med Parasitol.* 2013; 36(2): 75-87. (in Thai). ISSN 0125-4987.
- [12] Ngamjarus C, Pattanittum P. n4Studies Plus: application for sample size calculation in health science research. Version 1.4. App store; 2024. (in Thai).
- [13] Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform.* 2014; 48: 193-204. doi: 10.1016/j.jbi.2014.02.013
- [14] Obuchowski NA. Prospective studies of diagnostic test accuracy when disease prevalence is low. *Biostatistics.* 2002; 3(4): 477-92. doi: 10.1093/biostatistics/3.4.477
- [15] Ngamjarus C. Sample size calculation for health science research. 1st Ed. Khon Kaen, Thailand: Khon Kaen University Printing House; 2021. (in Thai).
- [16] Veterinary research and development center lower northern region by Maneephanchaoen, C. [internet]. Hidden dangers posed to people by fungi. [cited 2009 Feb 13]. Available from: <https://vrd-sn.dld.go.th/webnew/images/stories/service/Brochure/year59/Y13No49.pdf>. (in Thai).
- [17] Rianchainam, S., Kamluea, S., Damrongphokphan, J., Phaphan, R., Sihala, C., Ungpakorn, R. Sensitivity and specificity of diagnosis of Tinea versicolor in Thai patients. *Thai J of Dermatology.* 2009; 25(3): 619-23 (in Thai).
- [18] Mehregan DR, Gee SL. The cost effectiveness of testing for onychomycosis versus empiric treatment of onychodystrophies with oral antifungal agents. *Cutis.* 1999; 64(6): 407-10. PMID: 10626104
- [19] Nakashima T, Nozawa A, Ito T, Majima T, Yamaguchi H. Development of a new medium useful for the recovery of dermatophytes from clinical specimens by minimizing the carryover effect of antifungal agents. *Microbiol Immunol.* 2002; 46(2): 83-8. doi:10.1111/j.1348-0421.2002.tb02662.x
- [20] Sato T, Asahina Y, Toshima S, Yaguchi T, Yamazaki K. Usefulness of Wood Lamp for the Diagnosis and Treatment Follow-up of Onychomycosis. *Med Mycol J.* 2020; 61(2): 17-21. doi:10.3314/mmj.20-00004.

Comparing quality of life difference between diabetics and non-diabetics during the SARS-CoV-2 pandemic and post-pandemic: A web-based cross-sectional study India

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ABSTRACT

Background: The COVID-19 pandemic has irreversibly altered the global landscape, with far-reaching consequences for individuals' quality of life (QOL). In India, the series of lockdowns imposed to combat the pandemic presented unique challenges, exacerbating mental health concerns and amplifying anxiety and discontent among the population. Notably, the pandemic's impact on QOL has been unevenly distributed, with diabetic individuals potentially facing distinct challenges compared to their non-diabetic counterparts. Existing research in India has primarily focused on the health-related concerns of diabetic individuals, leaving a significant knowledge gap regarding the QOL of non-diabetic individuals during and following the pandemic. A comprehensive understanding of QOL differences between diabetic and non-diabetic populations is crucial for developing targeted interventions and improving overall well-being.

Objective: This study aims to address this gap by exploring and comparing the QOL of diabetic and non-diabetic individuals in India during and after COVID-19, providing valuable insights into the pandemic's impact on this critical aspect of health.

Materials and methods: A cross-sectional, comparative online-based survey study was conducted among 212 participants (diabetic and non-diabetic) aged 18 years and below 60 years visiting SRM General Hospital, between July and August 2021 during the COVID-19, and their self-reported scores were compared two years post-pandemic. A snowball sampling method was employed due to the pandemic's dynamic nature and online data collection feasibility. The RAND SF-36, a widely used 36-item quality-of-life questionnaire, was administered online via Google Forms and distributed through social media platforms and email invitations. Paired t-tests compared quality of life (QOL) during and after the SARS-CoV-2 pandemic. Multivariate regression analysis identified independent predictors influencing RAND SF-36 subscale scores.

Results: The study involved the collection of responses from a total of 212 participants, with a mean age of 46.61 ± 17.4 years. The RAND SF-36 questionnaire assessed the quality of life (QOL) during and after the SARS-CoV-2 pandemic. The results revealed significant differences in the general (45.8 ± 13.0 vs 64.9 ± 19.7 ; $p=0.001$) and mental health (53.5 ± 12.3 vs 62.7 ± 12.8 , $p<0.001$) between the two time periods. Furthermore, the study revealed age ($\beta=-0.369$, $p=0.004$, 95%CI [-0.608, -0.101]) and employment status ($\beta=-2.11$, $p=0.041$, 95%CI [-0.083, -4.139]) showed significant negative association with physical health-related component. In addition, the duration of comorbidities ($\beta=-5.326$, $p=0.047$, 95%CI [-11.408, -0.756]) gravely affected the mental health component, respectively.

Conclusion: Significant differences were noted in quality of life (QOL) between the SARS-CoV-2 pandemic period and after, with lower general health and mental health scores shown in diabetics as compared to non-diabetic individuals. Older

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age and unemployment were associated with worse physical health QoL, while the longer duration of comorbidities negatively impacted mental health QoL regardless of diabetes status. These findings suggest the pandemic substantially affected various aspects of QoL, underscoring the need for targeted interventions to support vulnerable populations.

Introduction

The impact on healthcare systems and communities was profound as COVID-19 cases surged worldwide, particularly in low and middle-income countries like India. India implemented comprehensive mitigation measures, including a nationwide lockdown from March 24, 2020, mandatory mask protocols, social distancing requirements, and travel restrictions, followed by a phased reopening and vaccination drive. These measures, while necessary for containing viral spread, created unique challenges for chronic disease management, particularly for the estimated 77 million Indians living with diabetes. The World Health Organisation's 2020 report, examining 163 countries, revealed that approximately half experienced significant disruptions in diabetes care and management of associated comorbidities during the pandemic. By March 11, 2021, India had recorded more than 11 million COVID-19 cases and 158,000 deaths, with diabetic patients facing disproportionate risks. The spread of COVID-19 in India was particularly concerning due to the country's large and densely populated areas, widespread poverty, high migration rates, and high prevalence of poorly controlled chronic conditions.^{3,4} Patients with diabetes faced unique challenges during the pandemic, requiring specialized attention from public health agencies. The disease burden for diabetic COVID-19 patients was distinctly higher, requiring more intensive monitoring protocols, extended hospital stays (averaging 4-7 days longer than non-diabetic patients), and increased critical care services. The case-fatality ratio was notably higher in individuals with diabetes (10.5%) compared to the general population (2.3%), highlighting their vulnerability during the pandemic.⁵⁻⁷

The impact extended beyond direct health outcomes to affect various aspects of quality of life. Diabetic patients reported greater difficulties in maintaining glycemic control due to restricted physical activity, dietary changes during lockdown, and limited access to healthcare services. Studies indicated that diabetic COVID-19 patients experienced higher rates of anxiety and depression, more significant disruptions in routine medical care, and greater economic burden compared to non-diabetic individuals. While both groups faced challenges from social isolation and economic uncertainties, diabetic patients reported additional stressors related to disease management and fear of COVID-19 complications.

Health-Related Quality of Life (HRQOL), defined as the general perception of individuals regarding their position in life and the impact of disease across physical, psychological, and social domains, showed particular deterioration among diabetic patients. While the pandemic caused an 8% reduction in perceived HRQOL worldwide, this reduction was more pronounced in the diabetic

population, particularly in psychological well-being and disease management domains. The focus during the pandemic was predominantly on COVID-19's impact on diabetic subjects, while non-diabetic individuals with other illnesses received relatively less attention.^{10,11} Individuals during the COVID-19 outbreak might experience extreme psychological cessation, i.e., loneliness, boredom, and anger, due to social distancing, quarantine, and isolation.¹² This subsequently causes psychological distress; studies have evidenced that psychological distress influences the quality of life. Previous studies reported that the COVID-19 outbreak caused mild psychological stress, i.e., physical and mental health, and this psychological stress influences quality of life.¹³

Since early 2022, as life began returning to normal, understanding the differential impact on diabetic versus non-diabetic populations has become crucial for developing targeted interventions and support systems. Web-based surveys have emerged as a feasible method for reaching target populations while maintaining social distancing protocols.¹⁴ Therefore, this study aims to evaluate and compare the quality of life between diabetic and non-diabetic individuals during and after the COVID-19 pandemic in India, providing valuable insights into how the lockdowns impacted various mental and general health aspects across these populations. To accomplish this comparison, we carried out an online web-based cross-sectional study in which we invited all diabetic and non-diabetic individuals we could reach. In addition, we assessed and compared differences in QoL in diabetic and non-diabetic individuals in India during and after the pandemic outbreak and examined the impact of the predictors, including age, presence of comorbidities, and occupation status, that have influenced QoL in diabetic and non-diabetic individuals.

Materials and methods

Study design and population

This cross-sectional study, an online-based survey, targeted individuals aged 18 years and older, comprising diabetic (DM) and non-diabetic (non-DM) participants. The study population consisted of adults from various social groups, such as teachers, students, researchers, Bankers, and development workers.

Sampling and sample size

A snowball sampling method was employed due to the pandemic's dynamic nature and because social distancing is a crucial issue during the COVID-19 outbreak. Two hundred and twelve participants (DM and non-DM) completed the online survey between July and August 2021 (during the COVID-19 pandemic) and again after three years post-pandemic outbreak. Given the unprecedented

nature of the COVID-19 pandemic and the rapid need to collect data, we prioritize timely data collection over a priori sample size determination; this study relied on a convenience sampling approach. The sample size was determined by the number of participants who responded to the online survey within a specified timeframe.

Inclusion criteria

The following inclusion criteria were: respondents aged 18 years above and below 60, diagnosed with diabetes with more than 3 months. Non-diabetic by self-reported (with medical reports, no history of diabetes) or by a physician and had admittance to a computer, smartphone, and internet to complete the questionnaire.

Exclusion criteria

1. Incomplete or partially completed questionnaires.
2. Participants provided adequate or consistent details.

Data collection

The research was conducted with ethical approval from SRM Medical College Hospital and Research Centre (approval number 2168/IEC/2020). The online questionnaire (RAND SF-36) was administered using Google Forms. It was shared with individuals visiting SRM Medical College and Research Hospital, Chennai, through online social media platforms, WhatsApp, and email invitations to reach them. The survey design prevented participants from modifying their responses post-submission, and completion time was estimated at 4-5 minutes. Informed consent was obtained through a statement mentioned in the questionnaire's section regarding the confidentiality and anonymity of the study before participation, emphasizing voluntary participation and confidentiality of responses. Reminder messages were sent to non-respondents every two days via social media platforms to ensure optimal participation. The initial data collection phase was conducted from July 23, 2021, to August 23, 2021, followed by a post-pandemic follow-up phase from May 1, 2024, to May 31, 2024, targeting the same participants across various regions of India. The uploaded survey materials were circulated using snowballing techniques. To avoid social desirability and response bias, we guaranteed that all the data would be used for academic and research purposes by ensuring respondents' privacy and anonymity.¹²

Instrument

The RAND short-form healthy survey (SF-36) questionnaire is an excellent tool for measuring health-related quality of life. It demonstrates strong psychometric properties, with internal consistency reliability (Cronbach's

alpha greater than 0.85, reliability coefficient greater than 0.75 for all dimensions as evidenced in previous study with its established content validity.⁽¹⁵⁾ The questionnaire entails of 36 questions and measures 8 health-related dimensions: physical functioning (PF), role limitation due to physical health (RP), social functioning (SF), bodily pain (BP), role limitation due to emotional health (RE), mental health and emotional well-being (MH), energy/fatigue (EF), role limitation due to emotional problems (RE), and general health (GH). Its validity and reliability have been established in several countries,¹⁶ including the Indian population,^{17,18} to assess health outcomes in various diseased populations.¹⁸ QoL is the composite of two domains: Physical health-related quality of life (PQoL) and mental health-related quality of life (MQoL).¹⁹

The physical domain comprises physical functioning, limitations due to physical pain, and general health. The mental subdomain includes social functioning and role limitation due to emotional and mental health. (20) Each subscale has a score range of 0 to 100. The replies were all scaled from one hundred to zero. Higher HRQOL ratings imply better health, while lower values suggest no health. For each SF-36 subscale, the average score was used to categorize HRQOL as either poor (ranging from 0 to 49) or good (ranging from 50 to 100).¹⁹ The scores signify the proportion of the maximum achievable score obtained.

Data analysis

The responses were collated in MS Excel 2021, and the composite scores were calculated by summing the subscale scores given in the questionnaire manual. Descriptive statistics such as frequency, mean, and standard deviation were used for other mean comparisons. Paired t-tests were performed to compare the different QOL scores and other domains during and after the COVID-19 outbreak. Multivariate regression analysis was performed to identify independent predictors influencing RAND SF-36 subscale scores.

Results

The table shows the study included 75 diabetic and 137 non-diabetic participants, totaling 212. The gender distribution indicates that 52.35% of the participants were male, and 47.65% were female. The duration of diabetes is further broken down into four categories: 3-6 months, 6-1 year, 5-10 years, and 10 years. The highest percentage (28%) of participants had diabetes for 5-10 years, followed by 3-6 months (18.7%) and 6-1 years (18.7%). Table 1 also provides information on the occupation status of the participants, including engineer, student, medical assistant, teacher, self-employed, and housewife.

Table 1. Demographic characteristics of the study participants.

Variables	Diabetic	Non-diabetic	Frequency	Percentage (%)
N	75	137	-	-
Male (N)	45	66	111	52.35
Female (N)	30	71	101	47.65
Duartion of diabetes (N)				
3-6 months	21	NA		28
6 -1 year	14			18.7
5-10 years	21			28
10 years	19			25.3
Employment status				
Engineer	3	9	12	5.2
Student	NIL	44	44	20.7
Medical assistant	6	8	14	6.6
Teacher	12	13	25	11.1
Self-employed	17	21	38	17.9
Housewife	21	20	41	20.7
Researcher	-	3	3	1.4
Retired	8	4	12	5.6
Others (tailor, radiographer,electricity maintenance, advocate)	7	6	13	6.13
Government service	6	4	10	4.7

Figure 1 represents the pie- chart showing that hypertension is the most common comorbidity, affecting 43% of the diabetic individuals in the study. Cardiac disease and other unspecified comorbidities (such as anemia, tuberculosis, and leukemia) are the next most prevalent, each affecting 14% of the participants. Renal disease, depression and anxiety, and thyroid disorders affect 9%, 10%, and 6% of diabetic individuals, respectively. Stroke

is the least common comorbidity, affecting 4% of the participants.

This information is crucial for understanding the overall health status of individuals with diabetes and the importance of comprehensive management strategies that address the primary condition and the associated comorbidities.

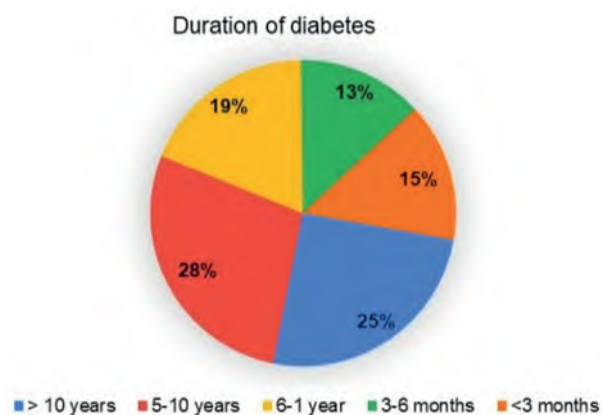


Figure 1. The prevalence of comorbidities among individuals with diabetes.

Figure 2 illustrates the duration and prevalence of pre-existing comorbidities among non-diabetic individuals. Figure 2A shows the pie chart depicting the duration of pre-existing comorbidities among non-diabetic participants. The distribution shows that 38% of participants reported comorbidities lasting 6-1 year, followed by 21% reporting conditions of <3 months duration, 17% with >10 years duration, 16% with 5-10 years duration, and 8% with 3-6 months duration. The distribution of self-reported

comorbidities among non-diabetic participants during the COVID-19 pandemic. Hypertension was the most prevalent condition (21%), followed by liver disease (16%), renal disease (15%), and equal proportions (13% each) of cardiac disease, depression & anxiety, and stroke. Thyroid disorders accounted for 5%, while other conditions (including anemia, TB, and leukemia) comprised 4% of reported comorbidities, as shown in Figure 2B.

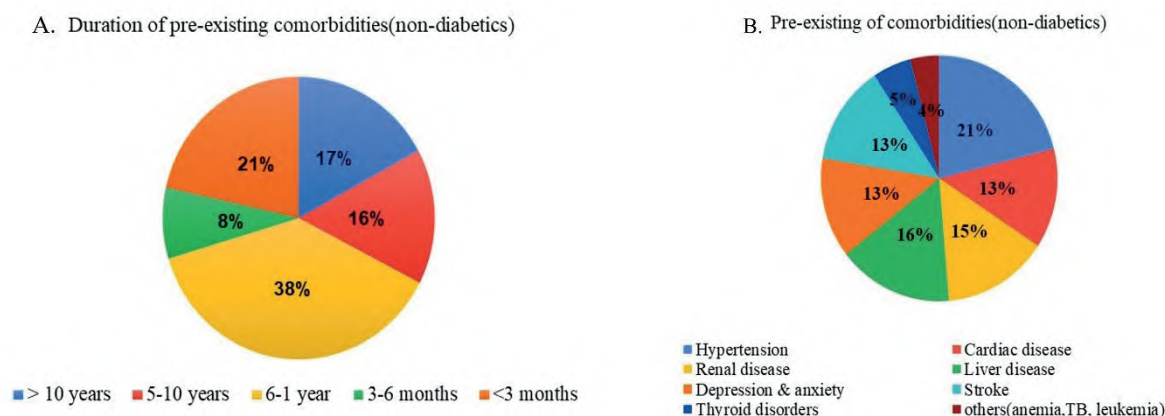


Figure 2. Duration of pre-existing comorbidities and prevalence of comorbidities among individuals with non-diabetics.

Table 2 represents a comparative analysis of the quality of life (QoL) domains in diabetic individuals during and after the SARS-CoV-2 outbreak. The data is organized into three primary columns: QoL during SARS-CoV-2, QoL after SARS-CoV-2, and the corresponding *p* value. The QoL domains assessed include general health (GH), physical functioning (PF), role limitation due to physical health (RP), role limitation due to emotional health (RE), energy/fatigue, mental health (MH), social functioning (SF), and bodily pain (BP).

The results (Table 2) show that the mean scores for most QoL domains in diabetic individuals improved significantly after the SARS-CoV-2 period compared to during the pandemic. The General Health (GH) score increased from 45.8 ± 13.0 during SARS-CoV-2 to 64.9 ± 19.7 after SARS-CoV-2, with a *p* < 0.001, indicating a statistically

significant improvement. Similarly, Physical Functioning (PF) and Mental Health (MH) scores also showed significant improvements, with *p* < 0.001. Role limitation due to physical health (RP) improved from 64.8 ± 33.5 to 54.9 ± 10.7 , with a *p* value of 0.021, suggesting a decrease in role limitations. The only domain that did not show a statistically significant change was Role limitation due to emotional health (RE), with a *p*-value of 0.299. These findings highlight the substantial impact of the SARS-CoV-2 pandemic on the quality of life of diabetic individuals and the subsequent improvements observed after the pandemic. The results underline the importance of comprehensive disease management strategies that address this vulnerable population's physical and mental well-being.

Table 2. Comparison of different quality of life domains in diabetics during and after the SARS-CoV-2 outbreak.

QoL Domain	QoL (during SARS-CoV-2)	QoL (after SARS-CoV-2)	<i>p</i> value
General health (GH)	45.8±13.0	64.9±19.7	<0.001
Physical functioning (PF)	60±6.2	69.4±18.9	<0.001**
Role limitation due to physical health (RP)	64.8±33.5	54.9±10.7	0.021*
Role limitation due to emotional health (RE)	65±22.5	69.7±24.2	0.299
Energy/fatigue	58.9±13.4	58.8±10.4	0.963
Mental health (MH)	53.5±12.3	62.7±12.8	<0.001**
Social functioning (SF)	57.6±22.5	50.3±15.3	0.029*
Bodily pain (BP)	67.5±19.2	70.7±21.1	0.357

Note: *significant *p* value, SD: standard deviation, **p* < 0.05 according to paired *t*-test.

Table 3 represents a comparative analysis of the quality of life (QoL) domains in non-diabetic individuals during and after the SARS-CoV-2 pandemic. The data is organized into five primary columns: QoL domains, QoL during SARS-CoV-2, QoL after SARS-CoV-2, and *p* value.

The QoL domains assessed include overall QoL (RAND SF-36), general health (GH), physical functioning (PF), role limitation due to physical health (RP), role limitation due to emotional health (RE), energy/fatigue, mental health (MH), social functioning (SF), and bodily pain (BP).

Table 3. Comparisons of different quality of life in the non-diabetic during and after the SARS-CoV-2 outbreak.

Domains	QOL (during SARS-CoV-2)	QOL (after SARS-CoV-2)	p value
Overall QOL(RANDSF-36)	57.49(9.01)	60.22(8.8)	0.034*
General health (GH)	41.2(13.9)	45.37(12.68)	0.037*
Physical Functioning (PF)	66.2(19.1)	71.6(18.9)	0.049*
Role limitation due to physical health (RP)	64.3(26.5)	73.3(30.79)	0.034*
Role limitation due to emotional health (RE)	62(31.03)	72.11(32.6)	0.030*
Energy/fatigue	49.8(13.8)	50.4(13.84)	0.770
Mental health (MH)	45.6(13.1)	43.3(14.0)	0.247
Social functioning (SF)	56.9(21.9)	60.5(21.53)	0.246
Bodily pain (BP)	70.0(19.1)	70(20.9)	0.995

Note: *significant p value, SD: standard deviation, **p<0.001, *p<0.05 according paired t test

The results show that most QoL domains improved in non-diabetic individuals significantly after the SARS-CoV-2 outbreak compared to during the pandemic. The Overall QoL (RAND SF-36) score increased from 57.49±9.01 during SARS-CoV-2 to 60.22±8.8 after SARS-CoV-2, with a p-value of 0.034, indicating a statistically significant improvement. The General health (GH) score improved from 41.2±13.9 to 45.37±12.68, with a p value of 0.037. Similarly, physical functioning (PF) also significantly improved, with a p value of 0.049. Role limitation due to physical health (RP) and Role limitation due to emotional health (RE) demonstrated significant improvements, with p value of 0.034 and 0.030, respectively. The remaining domains, including energy/fatigue, mental health (MH), social Functioning (SF), and bodily pain (BP), did not show statistically significant changes between the two-time points.

These findings highlight the considerable impact of the SARS-CoV-2 pandemic on the quality of life of non-diabetic individuals and the subsequent improvements observed after the outbreak. The results underline the

importance of addressing the general population's physical and mental well-being during and after such public health crises.

The results in Table 4 provide insights into factors influencing overall quality of life in mental health, general health, and role limitation to emotion. The analysis reveals that age had a significant association with several QoL domains. Specifically, age was an essential predictor of general health (GH), with a regression coefficient (β) of 0.420 and a p value of 0.001. The 95% confidence interval (CI) for the age effect on GH was [-0.252, -0.558], indicating that older age was associated with poorer general health-related QoL. Similarly, age was also significantly related to physical functioning (PF) (β = -0.331, p<0.001, 95% CI [-0.484, -0.179]), role-physical (RP) (β = -0.369, p=0.004, 95% CI [-0.608, -0.101]), fatigue (β = -0.239, p=0.013, 95% CI [-0.183, -0.486]), and social functioning (β = -0.312, p=0.001, 95% CI [-0.493, -0.132]), with older age being related to lower QoL in these domains.

Table 4. Multifaceted factors associated with poor QoL SF-36 subscales during and after the SARS-CoV-2 outbreak.

Variables	Predictor	β	B	p value	R ²	95% CI value
GH	Age	0.420	0.389	0.001*	0.392	-0.252,-0.558
	Employment status	-1.295	-0.155	0.035*		-2.518,-0.071
PF	Age	-0.331	-0.319	0.001	0.306	-0.484,-0.179
	Employment status	-1.691	-0.204	0.003		0.471,2.911
RP	Age	-0.369	-0.217	0.004*	0.256	-0.608,-0.101
	Employment status	-2.111	0.158	0.041*		-0.083,- 4.139
RE	Duration of comorbidities	-5.326	-0.136	0.047*	0.044	-11.408, -0.756
Energy/fatigue	Age	-0.327	0.324	0.001*	0.092	-0.183,-0.486
	Employment status	-1.303	-0.159	0.035*		-2.532,-0.109
SF	Age	-0.312	-0.257	0.001*	0.056	-0.493,-0.132
BP	Age	-0.173	-0.145	0.057	0.041	-0.352,0.005
	Comorbidities duration	2.113	0.131	0.058		-0.072,4.298

Note: GH: general health, PF: physical functioning, BP: bodily pain, RP: Role limitation due to physical health, RE: role limitation due emotional health, SF: social functioning, multivariate regression analysis, *significant p value, β : regression coefficient; B: stanardized regression coefficient.

In addition to age, the analysis also identified occupation status as a significant predictor of physical and mental health-related QoL components. Specifically, occupation status was significantly associated with GH ($\beta = -1.330$, $p = 0.035$, 95% CI [-2.518, -0.071]), RP ($\beta = 2.1465$, $p = 0.038$, 95% CI [-0.083, 4.139]), and the energy/fatigue domain ($\beta = -1.303$, $p = 0.035$, 95% CI [-2.532, -0.109]), suggesting that employment status was significant association with poor QoL in these areas. Furthermore, the study found that the duration of comorbidities was a substantial predictor of the role-emotional (RE) domain, with a regression coefficient (β) of -5.326 and a $p = 0.047$ 95% CI [-11.408, -0.756]. This indicates that the longer duration of comorbidities was associated with poorer emotional role-related QoL.

These findings contribute to understanding the multifaceted factors that influence physical and mental health-related QoL components, which can inform the development of targeted interventions and support strategies to improve the overall quality of life for individuals affected by various health conditions.

Discussion

The present study demonstrates significant improvements in multiple Quality of Life (QoL) domains following the SARS-CoV-2 period, with notable differences between diabetic and non-diabetic populations. In diabetic subjects, substantial improvements were observed in general health (GH) scores (45.8 ± 13.0 to 64.9 ± 19.7 , $p < 0.001$), physical functioning (PF), and mental health (MH) domains ($p < 0.001$). These findings align with research by Al-Sofiani *et al.*,²¹ who reported similar improvements in QoL metrics among diabetic patients post-pandemic, particularly in mental health domains. The significant enhancement in MH scores suggests successful adaptation to pandemic-related healthcare challenges and restoring routine diabetes management practices.

Non-diabetic subjects exhibited more modest but still significant improvements in their overall QoL scores (57.49 ± 9.01 to 60.22 ± 8.8 , $p = 0.034$) and specific domains such as general health (41.2 ± 13.9 to 45.37 ± 12.68 , $p = 0.037$). This pattern of improvement, while less pronounced than in diabetic subjects, corresponds with findings from Badinlou *et al.*, who observed gradual QoL recovery in the general population following the acute phase of the pandemic. The differential improvement rates between diabetic and non-diabetic groups might be attributed to the more structured healthcare engagement typically required for diabetic patients, resulting in better adaptation to post-pandemic healthcare delivery systems.²²

A notable finding was the lack of significant improvement in Role limitation due to emotional health (RE) among diabetic subjects ($p = 0.299$), while non-diabetic individuals showed considerable progress in this domain ($p = 0.030$). This disparity suggests persistent emotional challenges among diabetic individuals, possibly due to ongoing disease management burdens compounded by pandemic-related stressors. Similar findings were

reported by Meher D *et al.*, who identified sustained emotional health impacts among chronic disease patients post-pandemic.²³

The present study revealed that quality of life was significantly influenced by three independent factors: employment status and comorbidity duration, regardless of diabetic status. Notably, age emerged as a particularly robust predictor across multiple domains of the SF-36 HRQoL assessment, corroborating previous research findings.^{24,25} This relationship reflects how aging naturally leads to various physical changes in the body, increasing susceptibility to additional health conditions and contributing to an overall decline in health and well-being.²⁴ As people age, their HRQoL (health-related quality of life) leads to a gradual decline in their quality of life metrics.²⁶ This age-related decline was particularly pronounced in COVID-19, where SF-36 scores showed significant decrements among elderly populations.²⁷ This suggests that the aging process negatively affected the quality of life (QoL) scores of diabetes and non-diabetic individuals during the COVID-19 pandemic.²⁴

The predictive analysis revealed employment status as a significant determinant of physical and mental health-related QoL components, affecting General Health ($\beta = -1.330$, $p = 0.035$), physical role ($\beta = 2.1465$, $p = 0.038$), and Energy/Fatigue domains ($\beta = -1.303$, $p = 0.035$); this could be due to the lower income. The unemployment and retirement rates during the COVID-19 lockdown experienced an economic recession, which aligns with the findings of a previous study that demonstrated who identified employment status as a crucial modifier of pandemic-related QoL impacts.^{21,28} These factors may cause individuals to be more worn out than their economically and educationally advantaged counterparts. The negative association between comorbidity duration and role-emotional functioning ($\beta = -5.326$, $p = 0.047$) underscores the cumulative impact of chronic health conditions on emotional well-being, consistent with a longitudinal study by Abdullah Saeed *et al.*²⁹

Our study presents several notable limitations. While practical, the cross-sectional, web-based design limited our ability to fully assess the long-term effects of the COVID-19 pandemic on health-related quality of life (HRQoL). Future research employing a longitudinal approach would help validate and expand upon our findings.

Furthermore, our analysis did not incorporate several potentially influential variables that could affect quality of life outcomes. These include clinical markers like HbA1c, demographic factors such as education level, lifestyle factors including smoking and alcohol consumption, treatment modalities, and other health behaviors. Additionally, while our chosen methodology provided valuable insights, we acknowledge that using established tools like the WHO-QOL BREF might have offered more comprehensive measurements, particularly in assessing psychological health and social relationships among clinical populations. Future research should explore longer-term QoL trajectories and investigate the effectiveness of

targeted interventions for vulnerable populations identified in this study. Additionally, qualitative research could provide deeper insights into the mechanisms underlying the observed differences between diabetic and non-diabetic populations.

Conclusion

The COVID-19 pandemic had a significant impact on the quality of life for both individuals with diabetes and non-diabetics. However, the recovery trends differed between the two groups. After the pandemic, non-diabetic individuals experienced more substantial improvements in their quality of life compared to those with diabetes. Individuals with diabetes faced more significant challenges in managing their condition and experienced increased levels of anxiety and depression.

While both groups showed improvements in their quality of life, the discrepancy highlights the need for specialized assistance and resources for individuals with diabetes. This would help address their unique problems and facilitate more equitable recovery. The pandemic contributed to indirect economic burdens and reduced work productivity across both groups. However, the disproportionate impact on individuals with diabetes underscores the importance of tailored support to ensure an equitable post-pandemic recovery.

Conflict of Interest

There are no conflicts of interest

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References

- [1] World Health Organization. COVID-19 significantly impacts health services for noncommunicable diseases. Retrived 2024 November 13. Available from: <https://www.who.int/news/item/01-06-2020-covid-19-significantly-impacts-health-services-for-noncommunicable-diseases>
- [2] Ministry of Health and Family Welfare. Government of India. Retrived 2024 November 13. Available from: <https://mohfw.gov.in/>
- [3] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.* 2020;55(5):2000547. doi: 10.1183/13993003.00547-2020
- [4] Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, *et al.* The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. *The Lancet Global Health.* 2018 ; 6(12): e1352-62. doi: 10.1016/S2214-109X(18)30387-5
- [5] Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, *et al.* Clinical Features of COVID-19 and Factors Associated with Severe Clinical Course: A Systematic Review and Meta-analysis. *SSRN.* 2020; 3566166. doi: 10.2139/ssrn.3566166
- [6] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis.* 2020; 94: 91-5. doi: 10.1016/j.ijid.2020.03.017
- [7] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr.* 2020; 14(4): 395-403. doi: 10.1016/j.dsx.2020.04.018
- [8] Singh AK, Singh R. Does poor glucose control increase the severity and mortality in patients with diabetes and COVID-19? *Diabetes Metab Syndr.* 2020; 14(5): 725-7. doi: 10.1016/j.dsx.2020.05.037
- [9] Ghosal S, Bhattacharyya R, Majumder M. Impact of complete lockdown on total infection and death rates: A hierarchical cluster analysis. *Diabetes Metab Syndr.* 2020; 14(4): 707. doi: 10.1016/j.dsx.2020.05.026
- [10] Ghosh A, Arora B, Gupta R, Anoop S, Misra A. Effects of nationwide lockdown during COVID-19 epidemic on lifestyle and other medical issues of patients with type 2 diabetes in north India. *Diabetes Metab Syndr.* 2020; 14(5): 917-20. doi: 10.1016/j.dsx.2020.05.044
- [11] Verma A, Rajput R, Verma S, Balania VKB, Jangra B. Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. *Diabetes Metab Syndr.* 2020; 14(5): 1213-6. doi: 10.1016/j.dsx.2020.07.016
- [12] Khan AG, Kamruzzaman Md, Rahman MdN, Mahmood M, Uddin MdA. Quality of life in the COVID-19 outbreak: influence of psychological distress, government strategies, social distancing, and emotional recovery. *Heliyon.* 2021; 7(3): e06407. doi: 10.1016/j.heliyon.2021.e06407
- [13] Zhang Y, Ma ZF. Impact of the COVID-19 Pandemic on Mental Health and Quality of Life among Local Residents in Liaoning Province, China: A Cross-Sectional Study. *Int J Environ Res Public Health.* 2020; 17(7): 2381. doi:10.3390/ijerph17072381
- [14] Eysenbach G, Wyatt J. Using the Internet for surveys and health research. *J Med Internet Res.* 2002; 4(2): E13. doi: 10.2196/jmir.4.2.e13
- [15] Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, *et al.* Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ : Br Med J.* 1992; 305(6846): 160. doi: 10.1136/bmj.305.6846.160
- [16] Gandek B, Ware JE, Aaronson NK, Alonso J, Apolone G, Bjorner J, *et al.* Tests of data quality, scaling assumptions, and reliability of the SF-36 in eleven countries: results from the IQOLA Project. *International Quality of Life Assessment. J Clin Epidemiol.* 1998; 51(11): 1149-58. doi: 10.1016/s0895-4356(98)00106-1
- [17] Sinha R, van den Heuvel WJA, Arokiasamy P. Validity and Reliability of MOS Short Form Health Survey (SF-

- 36) for Use in India. Indian J Community Med. 2013; 38(1): 22-6. doi: 10.4103/0970-0218.106623
- [18] Kohli RM, Sane S, Kumar K, Paranjape RS, Mehendale SM. Assessment of quality of life among HIV-infected persons in Pune, India. Qual Life Res. 2005; 14(6): 1641-7. doi: 10.1007/s11136-004-7082-8
- [19] RAND Medical Outcomes Study. 36-Item Short Form Survey. Santa Monica, CA: RAND Corporation. Retrived 2024 June 3. Availablefrom: https://www.rand.org/healthcare/surveys_tools/mos/36-item-short-form.html
- [20] Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ. 1993; 2(3): 217-27. doi: 10.1002/hec.4730020305
- [21] Al-Sofiani ME, Albunyan S, Alguwaihes AM, Kalyani RR, Golden SH, Alfadda A. Determinants of mental health outcomes among people with and without diabetes during the COVID-19 outbreak in the Arab Gulf Region. J Diabetes. 2021; 13(4): 339-52. doi: 10.1111/1753-0407.13149
- [22] Badinlou F, Rahimian F, Hedman-Lagerlöf M, Lundgren T, Abzhandadze T, Jansson-Fröjmark M. Trajectories of mental health outcomes following COVID-19 infection: a prospective longitudinal study. BMC Public Health. 2024; 24(1): 452. doi: 10.1186/s12889-024-17997-x
- [23] Meher D, Kar S. Effect of pandemic on Quality of life in Diabetics (QOLID) assessment: Data from a teaching hospital in Bhubaneswar, Odisha, India. J Fam Med Prim Care. 2021; 10(10): 3780. doi: 10.4103/jfmpc.jfmpc_287_21
- [24] Ayalew M, Deribe B, Hussen S, Defar S, Gedefaw A. Quality of life among patients with chronic non-communicable diseases during COVID-19 pandemic in Southern Ethiopia: A cross-sectional analytical study. Front Psychiatry. 2022; 13: 855016. doi: 10.3389/fpsyt.2022.855016
- [25] Aschalew AY, Yitayal M, Minyihun A. Health-related quality of life and associated factors among patients with diabetes mellitus at the University of Gondar referral hospital. Health Qual Life Outcomes. 2020; 18(1): 62. doi: 10.1186/s12955-020-01311-5
- [26] Khorani H, Mohammadi F, Hosseinkhani Z, Motalebi SA. Predictive factors of Quality of Life in older adults during the COVID-19 pandemic. BMC Psychol. 2022; 10(1): 176. doi: 10.1186/s40359-022-00882-w
- [27] Romero Starke K, Petereit-Haack G, Schubert M, Kämpf D, Schliebner A, Hegewald J, et al. The Age-Related Risk of Severe Outcomes Due to COVID-19 Infection: A Rapid Review, Meta-Analysis, and Meta-Regression. Int J Environ Res Public Health. 2020; 17(16): 5974. doi: 10.3390/ijerph17165974
- [28] Zhang SX, Wang Y, Rauch A, Wei F. Unprecedented disruption of lives and work: Health, distress and life satisfaction of working adults in China one month into the COVID-19 outbreak. Psychiatry Res. 2020; 288: 112958. doi: 10.1016/j.psychres.2020.112958
- [29] Khan MdAS, Dalal K, Hasan M, Haque MMdA, Nusrat-E-Mozid, Hossian M, et al. The impact of comorbidity on the quality of life of people who recovered from COVID-19 in Bangladesh. IJID Regions. 2024; 11: 100351. doi: 10.1016/j.ijregi.2024.03.006

Evaluation of stress measurement using a wrist-worn device in volunteer subjects under Thai massage and cardio-exercise treatment

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ABSTRACT

Background: Stress is one of the key factors leading to mood disorders. Screening for stress through questionnaires and heart rate variability (HRV) required delicate consideration and expertise for result interpretation. Nowadays, wrist-worn devices, a non-invasive and real-time monitoring technology for assessing stress levels, are widely used.

Objective: To evaluate wrist-worn devices for stress measurement and assess the stress responsiveness of Thai massage (TM) and cardio-exercise in volunteers.

Materials and methods: Device verification was inferred before distributing the wrist-worn device to volunteers. Fifty volunteers were randomly assigned to 1.5 hours of TM and 4 weeks of cardio-exercise in zones 1-2 as a stress relaxation program. The stress response rate was compared among 3 different stress measurement tools: an HRV device, cortisol level, and a wrist-worn device.

Results: Wrist-worn devices' step count and heart rate function were verified within an acceptable error of <5% and well correlated with the HRV device before starting the assignment. The significantly decreased value of the stress after TM indicated the responsiveness for stress relaxation within an 85% response rate by HRV ($p < 0.001$) and 75% by wrist-worn devices ($p = 0.002$). Higher response outcomes were achieved from the cardio-exercise program, resulting in an 80% response rate by cortisol ($p < 0.001$), 83.3% by HRV device ($p = 0.001$), and 90% by the wrist-worn device ($p = 0.001$). Significant agreement of Kappa values for all paired devices under cardio-exercise reveals an acceptable similar response outcome from wrist-worn devices. The responsive outcome between TM and cardio-exercise programs in similar volunteer groups demonstrates no significant difference measured by HRV devices ($p = 0.375$) and wrist-worn devices ($p = 0.625$) using the McNemar test.

Conclusion: The data herein suggest that a wrist-worn device's stress monitoring provides satisfaction with real-time monitoring and long-term records comparable with HRV devices and cortisol measurements. Cardio exercise for 4 weeks of light and very light cardio is suggested as a continuous approach for stress relaxation. The TM program is a passive intervention that may help temporary relaxation compared to continuous cardio exercise according to subjective preference.

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Introduction

Stress-induced mood disorder has been found to increase in all ages according to the complexity of work constraints and living lifestyles. Common stress symptoms

can affect mood, thoughts, and feelings, such as anxiety, restlessness, lack of motivation, and memory problems. Chronic stress can lead to many health problems, from less severe, such as headaches, high blood pressure, muscle tension, fatigue, stomach upset, and obesity, to chronic diseases such as heart disease, stroke, and diabetes. Self-mental resilience plays an essential skill in handling stress. Knowing stress or self-monitoring of stress occurrence can help to manage its effects using possible stress relaxation approaches, for example, regular physical activity on most days of the week, meditation, yoga, tai chi, or massage.

The stress score by questionnaire is commonly used as a simple screening approach for stress. However, the diversity of ethnicity and society should be considered when assessing its reliability.¹ Cortisol, a hormone secreted from the adrenal gland, plays a vital role in the stress response. Stress activation along the hypothalamic-pituitary-adrenal (HPA) axis releases corticotropin-releasing hormone (CRH) from the hypothalamus.² Stimulation of the anterior pituitary by CRH prompts the release of adrenocorticotrophin hormone (ACTH), which triggers the adrenal cortex to secrete cortisol into blood circulation.³ Approximately a 9-fold increase in cortisol level was observed in stress compared to relaxed periods.⁴ Also, the cortisol level is routinely used to diagnose abnormalities along the HPA axis, such as Cushing's syndrome, adrenal insufficiency, and hormone replacement in Addison's disease. Acute cortisol change can be reliably measured in saliva and blood, cortisol in urine can be used to establish daily cortisol secretion, and cortisol in hair can be used to gather long-term cortisol levels over weeks or months.^{5,6} Assessment of cortisol in saliva captures acute cortisol production and is often used to measure daily stress because collection is relatively quick and easy. A high correlation between cortisol levels in blood and saliva has been reported.⁷ Moreover, the sensitivity and specificity of salivary cortisol accounted for over 90%.⁸ However, cortisol levels in the body fluctuate daily in response to stressors and circadian patterns that render salivary cortisol highest in the morning and lowest at night.^{7,9}

The increase of stress hormones in blood circulation leads to an increase in heart rate and the elevation of blood pressure. Any alteration of heart rate due to the stress response can contribute to the fluctuation of successive heartbeats or R-R interval, described as heart rate variability (HRV).⁹ HRV can be captured through different devices, including an electrocardiogram (ECG) with varying validity. An HRV device is equipped with an HRV measurement and analysis system, which reflects the heart activity and physiological changes and sensitivity to physical factors such as posture and movement while detected. Due to the data transformation from an ECG or HRV device, HRV is a sophisticated measurement that requires expertise for results interpretation. Collecting data reliably in a cost-efficient and ecologically valid way is difficult.

Nowadays, real-time monitoring and non-invasive methods for stress conditions have been introduced to

personal wearable devices. Wrist-worn device technology consists primarily of 3 primary sensors: a temperature sensor, a pulse rate sensor for physiological measurement, and an acceleration sensor for movement detection.¹⁰ A combination of more sensors and algorithms were introduced to devices to enhance performance, such as an infrared blood flow sensor, heart rate monitoring sensor, photoplethysmography sensor, optical sensor, etc. HRV or pulse shape variability (PSV) has also been introduced to the device, and the results for stress detection are displayed on the screen.¹¹ The development of small, reliable, cost-effective sensor devices has increased consumer access and interest. However, the accuracy of commercially available devices could be improved, and data quality assessment is needed.

Thai massage (TM) and cardio-exercise have been used for stress relaxation and office syndrome treatment.¹²⁻¹⁵ While the wrist-worn device has been well accepted as a friendly-to-use device for monitoring individuals' health, the validation of parameters acquired from the device remains limited.

This study evaluated wrist-worn devices harboring stress measurement functions compared to HRV devices and cortisol levels. TM and cardio-exercise were introduced as stress relaxation programs to volunteer subjects wearing wrist-worn devices, and the effectiveness of these stress-measuring devices was examined.

Materials and methods

Sample calculation

The absolute sample size for each intervention was found to be 22, which was calculated from the difference of two means formula. Participants were assigned to perform cardio-exercise zone 1 or 2 for 4 weeks. Stress parameters acquired from wrist-worn devices were substituted in the following equation:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \sigma_d^2}{\Delta^2}$$

The σ variance of stress parameters acquired from wrist-worn devices was 0.77, and the Δ mean difference of stress parameters acquired from wrist-worn devices was 0.46. The $Z_{\alpha/2}$ at 0.05 significant level was 1.96, whereas Z_{β} the 80% power was 0.84.

Study subjects

The study was conducted under the approval of the Ethical Committee for Human Research, Khon Kaen University, Khon Kaen Province, Thailand (HE641321). Due to the GCP guidelines, the confidential information of volunteers was included, and consent forms were obtained from all participants. Inclusion criteria were specified for the healthy individuals, who had to be diagnosed by physicians with normal blood pressure, no medicinal use, and no alcoholic consumption. On the other hand, individuals with a history of conditions including mental disorders, neuropathy, Cushing's syndrome, Addison's syndrome, chronic diseases, hyperthyroid, pregnancy, and medication onset were excluded. Subjects between the mid-working age of 18 and 40 who fit the inclusion criteria

were screened for stress baseline using Suanprung Stress Test-20 (SPST-20) questionnaires. This study included fifty volunteers with moderate stress (stress score >24 points) for further assignments.

Measurement parameters and devices

The stress index parameter was measured in terms of HRV using an HRV Analyzer SA-3000P (Medicore Inc., Korea). In contrast, PSV was retrieved from the wrist-worn device from Zensorium (Thailand) Ltd. HRV is reflected as a time-domain measurement of heartbeat fluctuation in terms of R-R interval in minutes. The involvement of the sympathetic autonomic nervous system (ANS) during stress increases heart rate, decreasing the R-R interval of HRV.⁹ The use of HRV assesses physical fitness and stress-coping ability. The physical stress index (PSI) reflects the load and pressure on the heart based on the R-R interval and heart rate, which indicates stress-related disorders such as fatigue, anxiety, dizziness, and depression.¹⁶ The PSV enables real-time monitoring of waveform alteration obtained from the photoplethysmography (PPG) sensor in the wrist-worn device. The alteration of heart rate and breathing during stress affects the pulse wave feature, which the PPG sensor can identify.¹⁷ The measurement of the PSV index will be displayed every 5 minutes. The alert of stress will indicate increased PSV. The computing of PSV from the device could be more transparent.

Cortisol level in saliva was also used as a biochemical-based, non-invasive method to compare the effectiveness of stress assessment devices. For both before and after the intervention, saliva was collected simultaneously before bedtime, as described by the manufacturer's procedure with the collection set (Salivette Cortisol, Sarstedt AG & Co. KG, Germany). After collection, the sample was immediately stored in a refrigerator (4-8°C) until use. The salivary cortisol was measured by electrochemiluminescence immunoassay (ECLIA) using a Cobas e801 Analyzer from Roche Diagnostics (Thailand) Ltd.

Wrist-worn device verification

Fifty wrist-worn devices were obtained from Zensorium (Thailand) Ltd. Before product delivery, the heart rate parameter between the Zensorium wrist-worn device and ECG was approved by the manufacturer and reported in mean absolute percent error (MAPE) with an acceptable value of $\leq 10\%$ under ANSI/CTA-2065 standard.¹⁸ The accuracy and precision of the 50 devices were retested for three functional modes, including step count, heart rate, and stress index, before being subjected to further experiments. Step count was compared between the displayed value on the screen device and the manual count. The difference between the manual count and the displayed values calculated inaccuracy regarding %bias. Imprecision was assessed in the percent of coefficient of variation (%CV) from 3 replicates of each device.

Heart rate measurement or pulse on the wrist-worn device was compared with manually counting the number of pulse beats at the wrist in one minute. The %bias and %CV were also calculated. In addition, the correlation of stress parameters obtained from wrist-worn devices and HRV devices among individual subjects (N=40) was also examined. The correlation coefficient and linear regression indicated the correlation between the two devices.

Responsiveness evaluation of stress relaxation by TM and cardio-exercise in volunteer subjects wearing wrist-worn devices

Regarding 50 recruited volunteers, only 40 subjects remained due to the dropout of subjects during the assignment, as shown in Supplement Table 1. These participants were randomly assigned to a short 1.5-hour Thai massage or 4-week cardio-exercise group as an independent group in a stress-relaxing program. Stress-responsive outcome was determined from the difference in stress values obtained before and after treatment. However, the final data of 36 volunteers (14 male and 22 female) remained. The age ranged from 20 to 38 years, with an average age of 28.6. The mean and standard deviation of BMI accounted 22.0 ± 3.67 .

Table 1. Verification data for imprecision and inaccuracy among the wrist-worn devices (N=50) used for step and heart rate parameters in this study.

Parameters	Precision (%CV)	Accuracy (%Difference or %Bias)
Step count (N=50)		
Mean	1.69	1.25
Range (min-max)	0-4.97	-3.50-2.00
Heart rate (N=50)		
Mean	1.25	1.38
Range (min-max)	0-3.21	-4.5-3.5

Thai massage

A total of 24 volunteers were assigned to receive regular TM treatment for 1.5 hours at the AMS Wellness Service Centre, Faculty of Associated Medical Science, Khon Kaen University. To minimize the variability of TM practitioners, only 1 staff member was assigned to treat all volunteers. Four volunteers were excluded due to incomplete data log records of the wrist-worn device, resulting in only 20 data obtained.

Stress parameter measurements were compared before and after TM was acquired from wrist-worn and HRV devices.

Cardio-exercise

A total of 30 volunteers were assigned to exercise according to their favorite program, e.g., running, badminton, etc., for four weeks to reach the acquired definition of cardio-exercise zones 1 or 2. The exercise period and frequency can be checked using data log records in a wrist-worn device to meet the criteria of 150 minutes per week.

Stress levels via HRV and wrist-worn devices were monitored during the period, as summarised in the experiment design in Figure 1. Moreover, cortisol levels in saliva were investigated on the starting date (week 0) as a baseline value and at the 4th week as the end point of intervention.

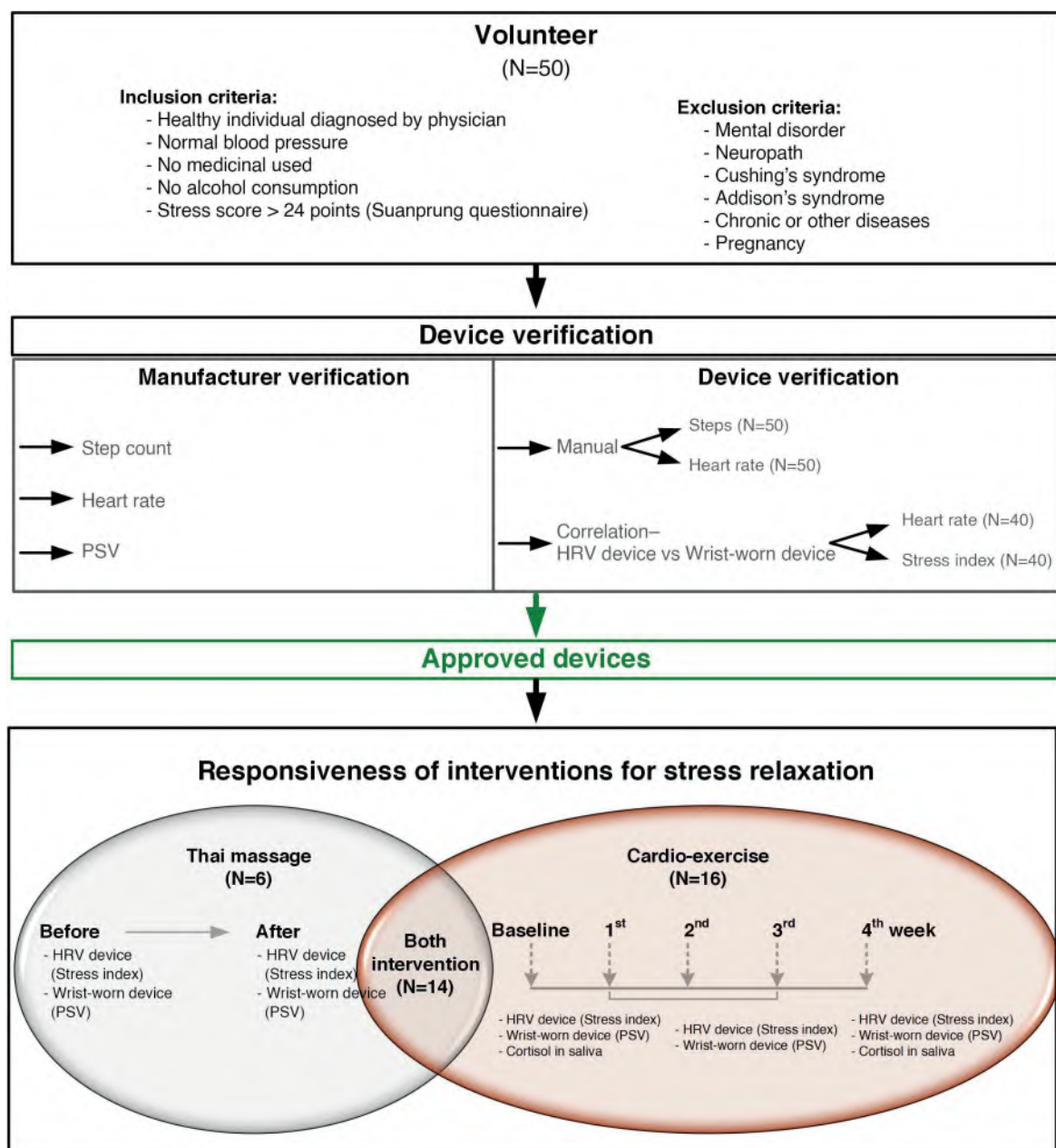


Figure 1. Experimental design of the study.

Both interventions at different time

Among two interventions, 14 volunteers were selected to perform TM and cardio-exercise. To minimize the effect of each intervention in this group, volunteers who underwent TM once for at least 4 weeks prior were assigned to perform the cardio exercise.

The change in stress level between after and before intervention acquired from each detection method were recorded. A decrease in stress level after an intervention is indicated as a response case. On the other hand, an increased value and no change value after intervention indicated a non-response case.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics v.28 under Khon Kaen University license (IBM Corporation, IL, USA). The difference in stress levels obtained from each measurement method was calculated by subtraction before and after applying the intervention. The Shapiro-Wilk test was used to test the normality of differences. The statistical significance of stress values before and after intervention was determined using a paired t-test in the parametric dataset. At the same time, the Wilcoxon Signed Rank test was used for the nonparametric dataset with $p \leq 0.05$.

McNemar statistic was used to compare the conformity of the response outcome between TM and cardio-exercise in the same volunteers.

Cohen's kappa was introduced to determine the agreement of responsive outcome through each intervention (cardio-exercise and TM) using different stress measurement methods (cortisol, HRV, and wrist-

worn device). Levels of agreement, including none, minimal, weak, moderate, strong, and almost perfect, were classified by kappa values of 0-0.2, 0.21-0.39, 0.40-0.59, 0.60-0.79, 0.80-0.90, and >0.90 , respectively,¹⁹ while statistically significant responsiveness was indicated by a $p \leq 0.05$.

The power of the test was calculated to determine the sample size in each study group. A power of 80% or more is considered a sufficient sample size.

Results

Wrist-worn device verification

A total of 50 obtained wrist-worn devices were evaluated before being given to volunteers in two parameters: step count and heart rate functions. Averaged %CV and averaged %bias at 1.69% and 1.25% were observed for step count, whereas 1.25% and 1.38% were observed for heart rate function (Table 1). All wrist-worn devices were accepted as having acceptable imprecision and inaccuracy of $\leq 10\%$. These data agreed with the certificate of the product by Zensorium® wrist-worn devices using the comparison of heart rate measurement with ECG and reported in MAPE. Percent MAPE estimated from 6 physical activities, including walking, running, sitting, typical activities, cycling, and sleeping, were 7.41%, 8.48%, 2.40%, 5.71%, 9.71%, and 1.54%, respectively.

The heart rate and stress index of the wrist-worn devices were also compared with that of the HRV device (N=40). A positive and significant correlation of heart rate was found with $r = 0.906$, $p < 0.001$, while stress index by the wrist-worn devices gave a lower correlation with $r = 0.404$, $p = 0.01$ (Figure 2).

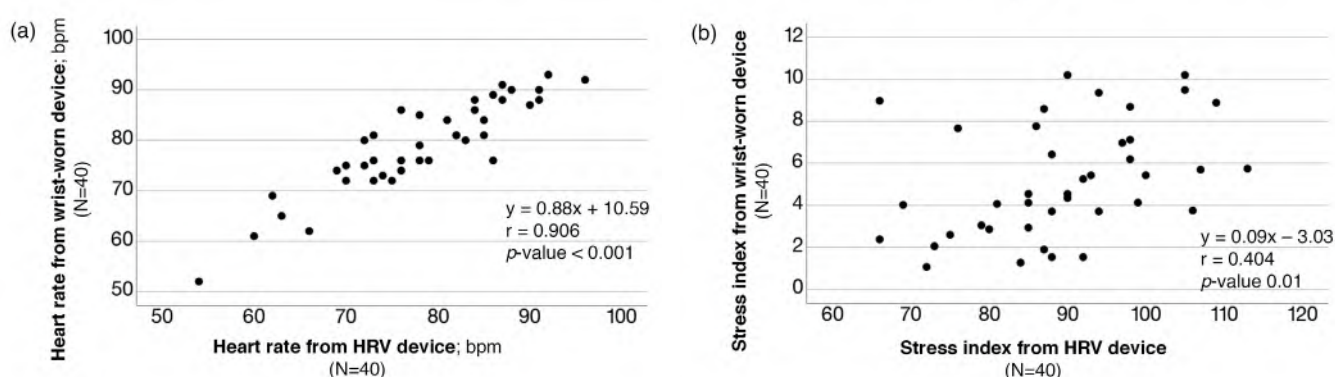


Figure 2. Correlation between heart rate (a) and stress parameters (b) acquired from the HRV device and wrist-worn device.

Agreement of stress-responsive outcome between wrist-worn devices and other devices

Stress monitoring parameters, including salivary cortisol level, stress index from HRV device, and PSV from wrist-worn device acquired from each subject, were categorized into response and non-response cases concerning the two different relaxation intervention programs, TM and cardio-exercise, as shown in Table S1. The response outcome is defined as the decreased stress parameters after intervention, whereas non-response is indicated whenever no change or increased stress values are found after intervention.

Methods were paired and compared using Cohen's kappa to evaluate the agreement level, as shown in Table 2.

Cortisol as a diurnal variation marker was excluded in TM because only 1.5 hours of TM was conducted as a short-term treatment. The wrist-worn devices demonstrated a high percentage of agreement at 80% under the TM program and 86.67-90% under the cardio-exercise program compared to other methods. A significant Kappa value was found for all paired devices under cardio exercise, indicating a similar response from wrist-worn devices. Higher agreement on stress-responsive outcome was found with moderate kappa ($p < 0.001$) between the wrist-worn devices and cortisol values compared to weak kappa ($p = 0.014$) by the HRV device. In addition, both HRV and cortisol levels, as compared to methods, were found to have significantly moderate agreement ($p < 0.001$).

Table 2. Agreement analysis for stress responsiveness among different stress measurement methods.

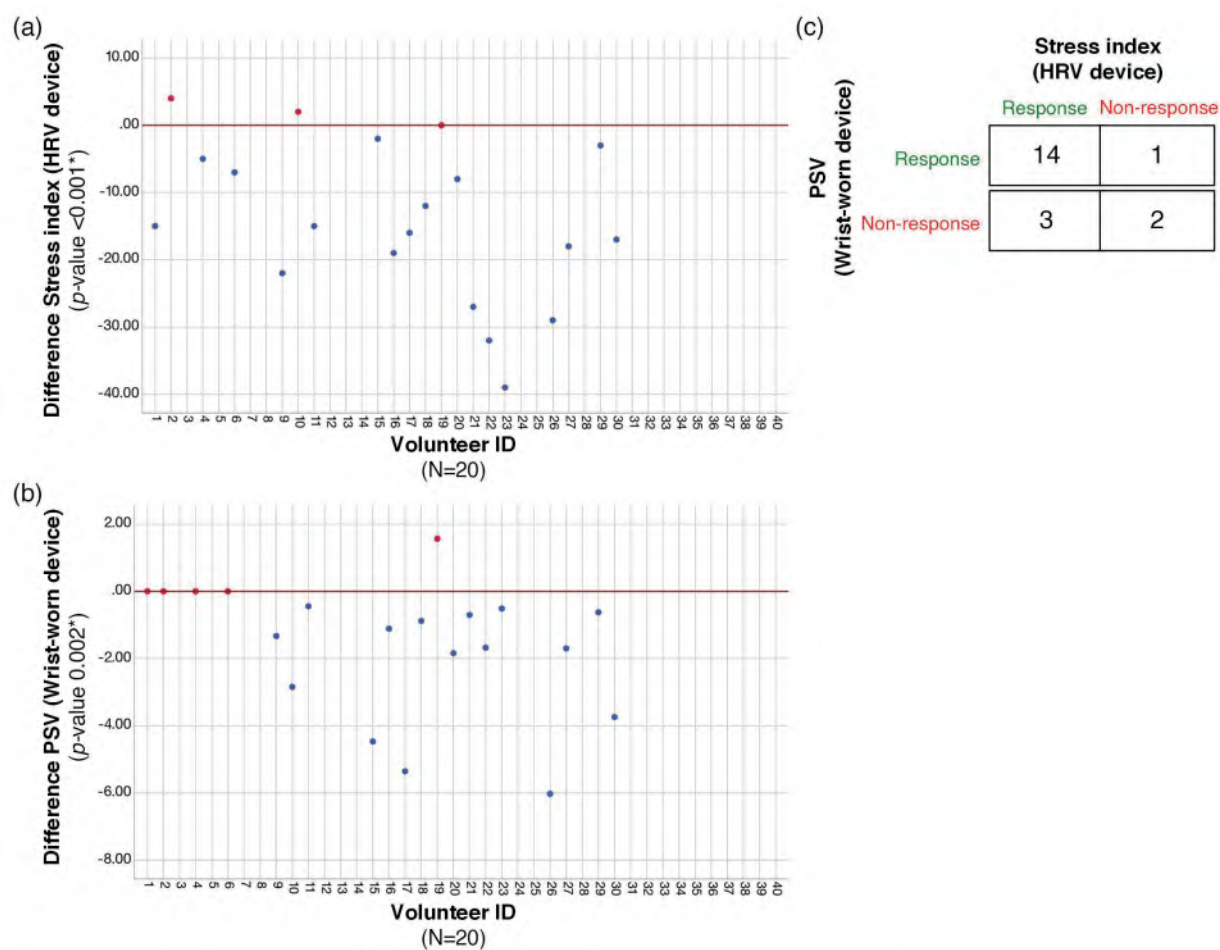
Comparison	%Agreement*	Kappa value (Level of agreement)	p value
Thai massage (N=20)			
Wrist-worn device vs HRV	80%	0.385 (Minimal agreement)	0.071
Cardio-exercise (N=30)			
Wrist-worn device vs Cortisol	90%	0.615 (Moderate agreement)	<0.001
Wrist-worn device vs HRV	86.67%	0.429 (Weak agreement)	0.014
HRV vs cortisol	90%	0.667 (Moderate agreement)	<0.001

Note: *The percentage of agreement for each pair of devices was calculated from the number of similar outcomes in both response and non-response cases.

The comparison of intervention programs for stress relaxation in volunteers wearing wrist-worn device

Stress measurement among 20 volunteers was monitored before and after being subjected to the TM program. Statistical significance of the different stress values after the intervention was found with both HRV ($p < 0.001$) and wrist-worn devices ($p = 0.002$), as shown in Figures 3a-3b. The decreased value of the stress index after TM indicated significant responsiveness for stress relaxation. HRV gave an 85% response rate (17/20), whereas a lower response rate of 75% (15/20) was found from wrist-worn devices (Figure 3c). A total of 3 cases of non-response outcomes (V2, V10, and V19) were found

from the HRV device, while 5 cases of non-response (V1, V2, V4, V6, and V19) were found by the wrist-worn device (see also supplement Table S1). Comparing the 2 methods, 14/20 individuals provided consensus response outcomes, while another 2/20 individuals were non-response to the intervention, accounting for 80% (16/20) conformity outcomes. The remaining 4 individuals (V1, V4, V6, and V10) with different outcomes revealed a 20% discrepancy between the two methods. Among the discrepancy outcomes, 3 cases (V1, V4, and V6) except V10 resulted in non-response detected by the wrist-worn device. This result indicates a higher sensitivity of HRV devices to detect stress than wrist-worn devices.

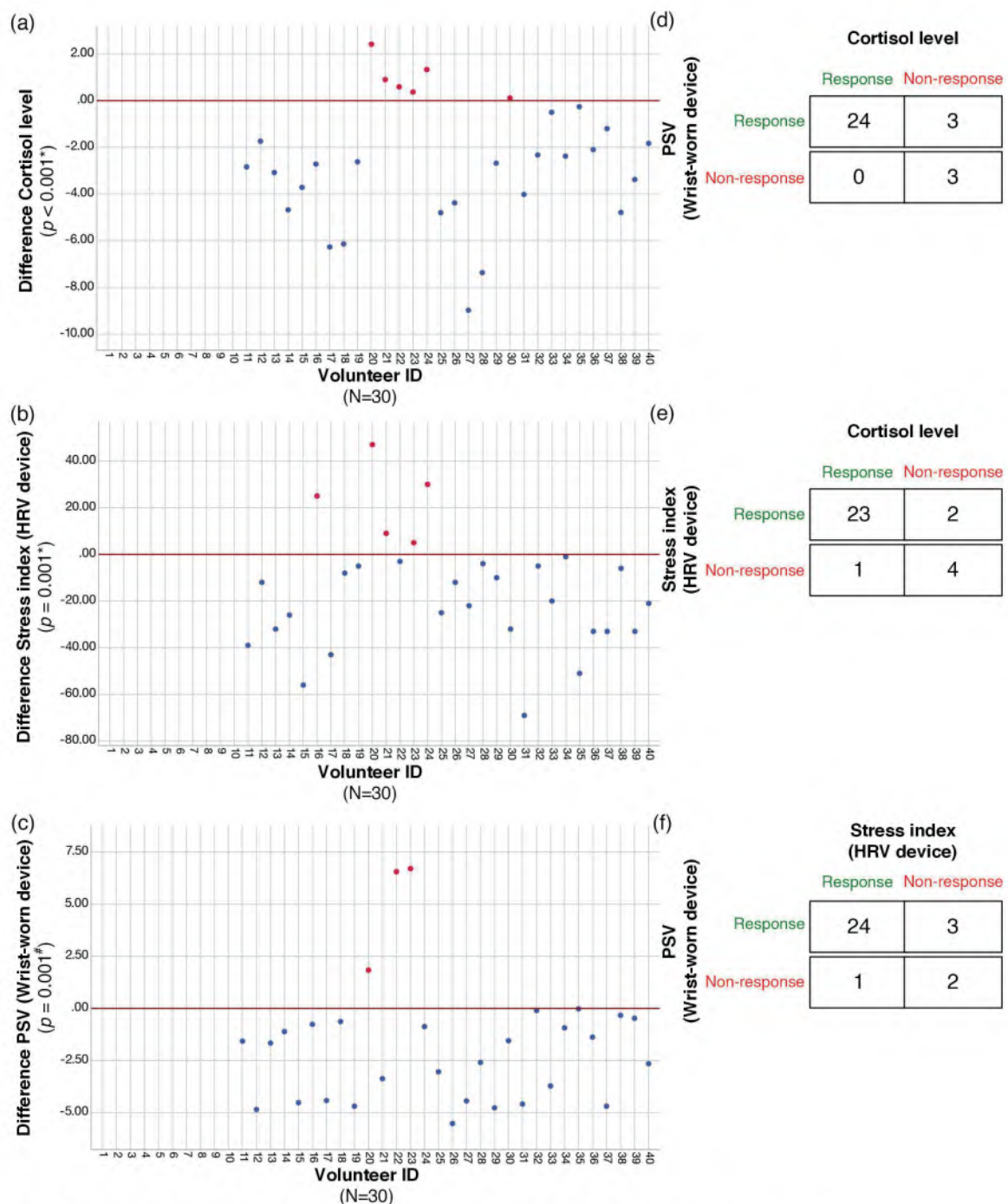


*Pair t-test was used to compare the difference of stress responses before and after intervention.

Figure 3. Responsiveness of stress relaxation in volunteer subjects who acquired Thai massage intervention. The response outcome is defined as the decreased stress value after intervention, whereas non-response is indicated whenever no change or increased stress values are found after intervention. Spots indicate the difference in stress indication measured by (a) the HRV device and (b) the wrist-worn device, while blue indicates a response (negative value below zero line) and red indicates a non-response (zero or positive value at and upper the zero line), and (c) presents a confusion matrix comparing the outcome between HRV and wrist-worn device after treatment.

Figure 4 shows significant stress response outcomes after 4 weeks of the cardio-exercise program, resulting in 80% (24/30) response rate (blue dot) by cortisol level ($p < 0.001$, Figure 4a), 83.3% (25/30) response rate by HRV device ($p = 0.001$, Figure 4b) and 90% (27/30) response rate by wrist-worn device ($p = 0.001$, Figure 4c). The consensus outcome for stress response between method-pairing is

summarised in Figures 4d-4f. Figure 4d indicates a 10% discrepancy with 3 cases (V21, V24, and V30) between wrist-worn devices and cortisol pairing and an equal 10% discrepancy between HRV and cortisol pairing (Figure 4e), whereas 4 cases (V16, V21, V22 and V24) or 13.3% discrepancy was found when comparing wrist-worn devices and HRV (Figure 4f).



*Pair t-test was used to compare the difference of stress responses before and after intervention.

*Wilcoxon signed rank test was used to compare the difference of stress responses before and after intervention.

Figure 4. Discrepancy of response outcome for stress relaxation in 30 volunteer subjects who performed cardio-exercise intervention measured by (a) cortisol, (b) HRV device and (c) wrist-worn device. A blue dot indicates response (negative value below zero line), while a red dot indicates non-response (zero or positive value at and above the zero line). Two by two tables of paired methods were summarised between wrist-worn device & cortisol (d), cortisol & HRV device (e) and wrist-worn device & HRV device (f).

To minimize the confounding from different baselines of stress values in each subject, 14 volunteers were fixed and assigned to TM and cardio exercises using a similar stress measurement device, as shown in Figure 5. To avoid the interaction of 2 relaxing programs, a wash-out period of 4 weeks apart was strictly followed.

Out of a total of 14 volunteers, 5 cases (V16, V19, V20, V21, and V23) exhibited different outcomes, resulting

in a 35.7% discrepancy response between TM and cardio-exercise when the HRV device monitored stress without significant difference (Figure 5a-5b, $p=0.375$). Only 4 cases (V19, V20, V22 and V23) showed a 28.6% discrepancy when using wrist-worn devices (Figure 5c-5d, $p=0.625$). No significant difference between TM intervention (Figure 5a-5c) and cardio-exercise (Figure 5b-5d) measured by other devices was also found ($p>0.05$) using the McNemar test.

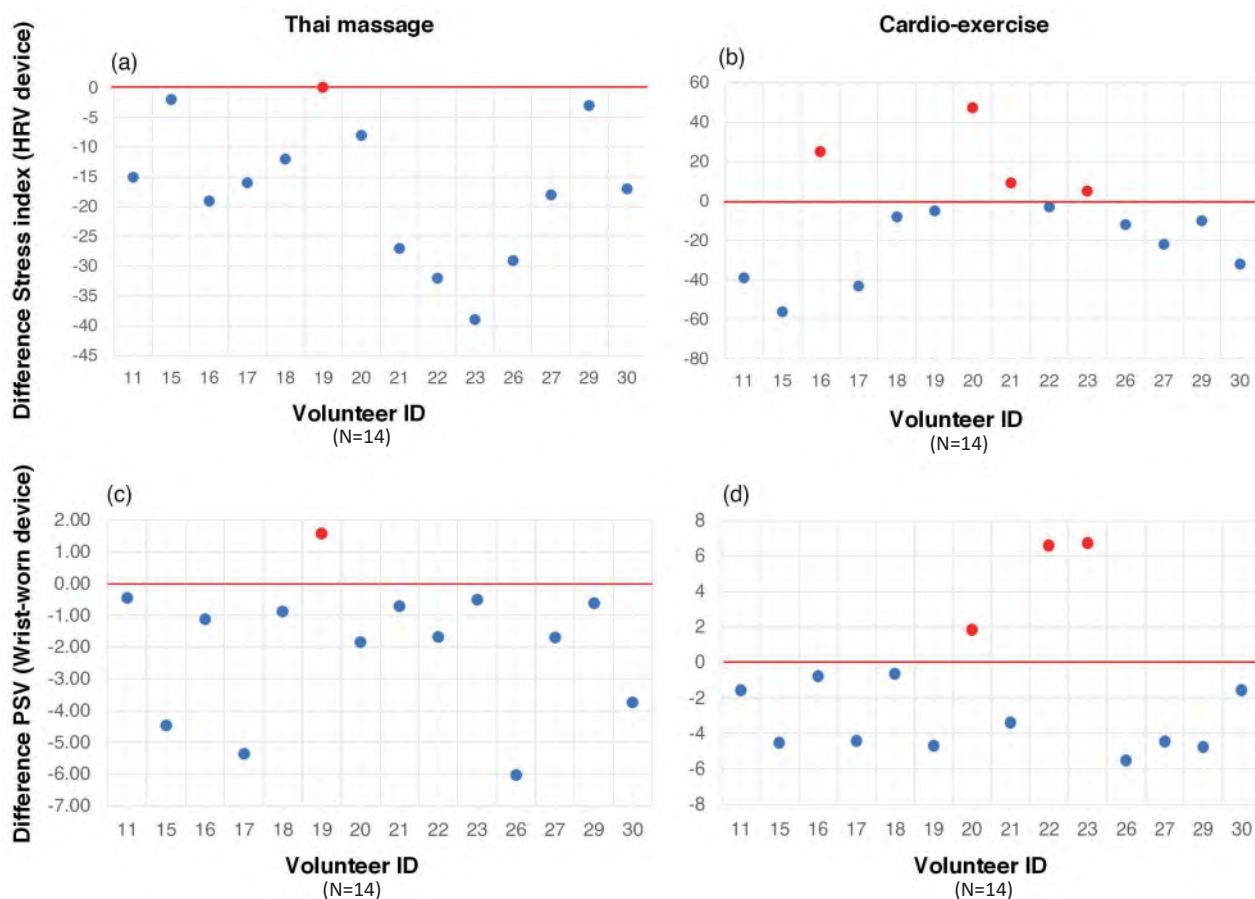


Figure 5. Disconformity outcome between Thai massage and cardio-exercise program in similar volunteer groups (N=14) demonstrates no significant different measured by HRV device (a and b, $p=0.375$) and wrist-worn devices (c and d, $p=0.625$) using McNemar test.

Line plots of multi-point stress monitoring data using an HRV and wrist-worn device were compared among 14 volunteers for 4 weeks of cardio-exercise, as shown in Figure 6. The response rate detected by HRV and wrist-

worn devices was 71.4% (10/14) and 78.6% (11/14), respectively. This data confirmed comparable outcomes dependent on a relaxation program using either wrist-worn or HRV devices.

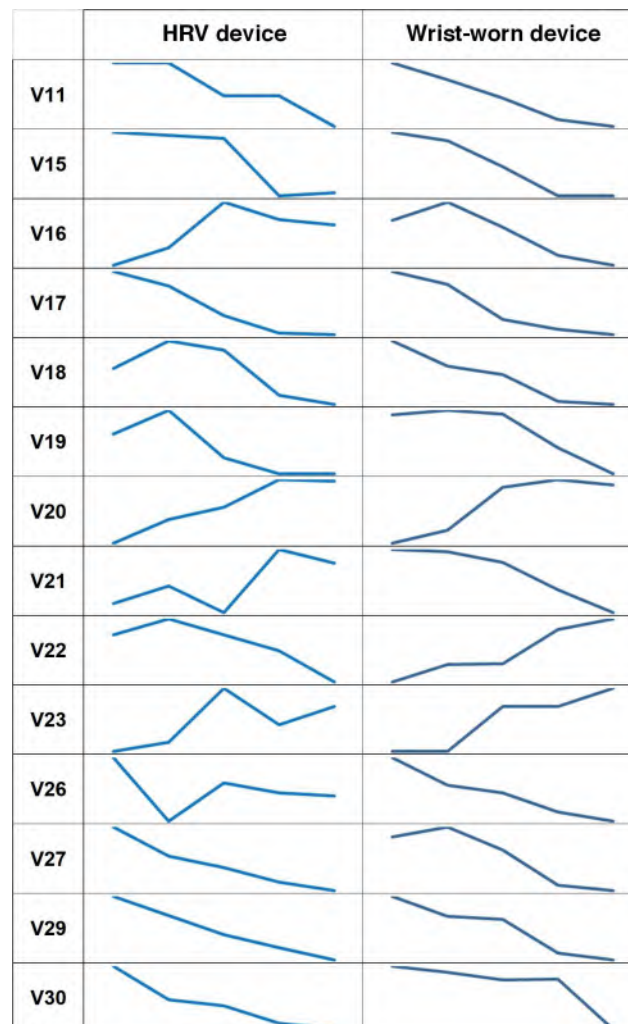


Figure 6. Stress monitoring of 14 subjects receiving 4 weeks of cardio-exercise program measured with 2 different methods including wrist-worn device (PSV) and HRV device.

Discussion

The performance of all wrist-worn devices included in this study was qualified with inaccuracy and imprecision of less than 5% for step count and heart rate function following the ANSI/CTA-2065 standard. Heart rate measurement by the wrist-worn device was found to have a reasonable correlation ($r=0.906$) with the HRV device. Taken together with the acceptable 10% MAPE certified by the manufacturer, all wrist-worn devices were approved for further investigation in the study. Moreover, a comparison study was conducted against different wearable devices in heart rate and energy expenditure parameters.²⁰ Variable levels of accuracy for heart rate measurement were activity-dependent, ranging from 2.44-10.76%. Although stress measurement between wrist-worn devices and HRV devices was found to have a lower correlation ($r=0.404$), the difference in stress measuring units can be explained by the poor correlation between

both devices. HRV detects heart rate variables, but the wrist-worn device detects pulse shape variables.^{11,21} The concordance of responsive outcome between TM and cardio-exercise using different devices by Kappa analysis is summarised in Table 2, indicating that significant agreement was found in wrist-worn devices with HRV and cortisol in the cardio-exercise program. Still, considerable agreement was being reached regarding the TM program. These data suggest that the wrist-worn devices provided an excellent and correlated responsiveness outcome with HRV and cortisol as the standard method. The results of the Kappa analysis confirmed the consensus outcome of stress response between method pairing, which showed HRV and cortisol provided comparable standard methods to evaluate the performance of wrist-worn devices under a cardio-exercise program. A similar finding also previously suggested an accuracy of HRV at 75% compared to EEG at 77.9%.²²

Since the Kappa value demonstrated different agreements of stress-responsive outcomes among devices, the confounding factors from individual volunteers may contribute to the measurement discrepancy among controlled intervention programs. For TM, an HRV device can detect a higher response rate (17/20) than a wrist-worn device (15/20), suggesting that the HRV device is more sensitive to detecting changes in stress than a wrist-worn device. This finding can also be explained by the more comprehensive detectable range of HRV (60-120 units) compared to the smaller detectable range of PSV (1-10 units). In addition, the ineffectiveness of TM found in V2, V10, and V19 was explained by the experience of TM. V2 and V10 were unfamiliar with TM intervention, which may result in resistance to stress relaxation.

In contrast to V19, who suffered from office syndrome, only a short 1.5-hour TM may be insufficient to handle the stress.²³ Notably, the responsive outcome in cardio-exercise using a wrist-worn device gave the best response rate detection (27/30) compared to the HRV device (25/30) and cortisol (24/30). This finding suggests that a wrist-worn device for real-time monitoring can deliver more data supporting the actual stress for 4 weeks of intervention than the discrete monitoring of HRV devices and endpoint monitoring of cortisol.

To minimize the confounding effects among subjects underlying different stress baselines, a group of 14 subjects was assigned to both programs at various times (4 weeks apart). The comparison of stress responses of TM and cardio-exercise indicated no statistically significant difference between interventions with fixed devices and different devices with fixed intervention. However, 4 (V19, V20, V22, and V23) out of 14 (28.5%) shared the typical discrepant rate, implying that different outcomes may occur according to subject dependence on the relaxation program (Figure 5). Among the discrepancy cases, V19 suffered from long-term office syndrome, representing non-response outcomes by short period TM, while V20 carried over the restricted cardio-exercise zone 2; V22-V23 performed exercise longer than the recommended period (>200 min/week), which may have caused muscular strain and muscular fatigue. A heavy cardio zone may cause inappropriate muscle strain or exhaustion, resulting in relaxation resistance.²⁴ Moreover, various factors may affect stress levels, including the amount and duration of stress, genetic components, and patient history.²⁵ The success rate of stress relaxation with exercise depends on the duration period of regular exercise, which creates an accumulation effect compared to TM. Although TM is a traditional passive treatment with short-term response, the duration period and regular treatment might be important factors for successful response rates. The stress relaxation mechanism of cardio-exercise is associated with the neuroendocrine response to modulate cortisol hormone via an inactivation of cortisol into cortisone, an inert steroid. Increased anandamide (AEA) level, an endocannabinoid (eCB) during exercise, is a key induced increment in brain-derived neurotrophic factors that activate endorphin secretion, a positive mood hormone.

In addition, muscle activity during exercise increases tryptophan's uptake, crossing the blood-brain barrier and leading to increased serotonin, a neurotransmitter for sound emotional processing and memory function.²⁶

To date, the American College of Sports Medicine (ACSM) guidelines have recommended that a minimal exercise program should consist of at least 20-30 min/per day, 3-5 days/week, for a total of 75-150 min/per week to develop and maintain cardiovascular fitness and reduce body fat.²⁷ A similar finding demonstrated susceptibility to stress reduction after zone 2 cardio-exercise (at least 30 min/day, 3-5 days/week for 8 weeks) in 30 nurse subjects and 55 physical therapy students.^{15,28}

Trend analysis demonstrated that wrist-worn devices can provide slightly higher response rates than HRV. All data are recorded in real-time and kept in a data log, enabling a superior advantage for stress monitoring in personal use.

In this study, TM intervention was limited to only one short duration (1.5 hours), while the cardio exercise was delivered for 4 weeks. Thus, the cortisol could not be measured in TM intervention. Also, Kappa value of TM gave minimal agreement compared to moderate agreement of cardio-exercise. Moreover, cardio-exercise is recommended in cardio zones 1-2 but not limited to any specific sport. Some volunteers dropped out of the study due to insufficient periods of cardio zone 1-2. Some volunteers carried out heavy cardio zone 3, resulting in an exhausted status, which resisted the stress relaxation.

Moreover, more studies on wrist-worn devices using PPG sensors in the market are needed due to the limitation of raw data access. Processed data from most wrist-worn, for example, Apple, Garmin, or Fitbit bit, can be extracted using the Application Programming Interface (API); direct access to raw data is impossible. The performance evaluation study of standard wearable sensors for stress detection, including PPG sensors.²⁹ This study compared seven common wearable sensors by collecting data during baseline, stress, recovery and cycling from 32 participants. Machine learning algorithms were used to classify stress from all wearable sensors. The results demonstrated no significant different in accuracy. Therefore, the user's expectation preference and wearable comfort are considered when selecting a wearable for stress detection.

Conclusion

The current analysis indicated that wrist-worn devices can help plan health assessment strategies and reduce stress. Stress monitoring by wrist-worn devices illustrates good performance comparable with HRV devices and cortisol levels. Stress measurement using a wrist-worn device offers advantages in real-time monitoring and long-term recording. Cardio exercise over 4 weeks was a better stress-relaxed approach than 1.5-hour TM. This finding supports the effectiveness of the proposed cardio-exercise program as a continuous and long-term activity with light and very light cardio zones. A heavy cardio zone may cause inappropriate muscle strain or exhaustion, increasing stress levels instead of

relaxation. Therefore, the suitable duration and exercise zone might be individually adjusted. Moreover, the TM program is exerted as a passive intervention that may help temporary relaxation compared to continuous cardio exercise according to subjective preference.

Conflict of interest

The authors declare no conflicts of interest.

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References

- [1] Shahid A, Wilkinson K, Marcu S, Shapiro CM. Perceived stress questionnaire (PSQ). In: Shahid A, Wilkinson K, Marcu S, Shapiro CM, editors. STOP, THAT and one hundred other sleep scales [Internet]. New York, NY: Springer New York; 2011 [cited 2023 Oct 21]. p. 273-4. Available from: http://link.springer.com/10.1007/978-1-4419-9893-4_64
- [2] Filatova EV, Shadrina MI, Slominsky PA. Major depression: One brain, one disease, one set of intertwined processes. *Cells*. 2021; 10(6): 1283. doi: 10.3390/cells10061283.
- [3] Russell G, Lightman S. The human stress response. *Nat Rev Endocrinol*. 2019; 15(9): 525-34. doi: 10.1038/s41574-019-0228-0.
- [4] Cay M, Ucar C, Senol D, Cevirgen, F, Ozbag D, Altay Z, et al. The effect of cortisol level increasing due to stress in healthy young individuals on dynamic and static balance scores. *North Clin Istanbul*. 2018; 5(4): 295-301. doi: 10.14744/nci.2017.42103
- [5] Remer T, Maser-Gluth C, Wudy SA. Glucocorticoid measurements in health and disease - Metabolic implications and the potential of 24-h urine analyses. *Mini Rev Med Chem*. 2008; (2): 153-70. doi: 10.2174/138955708783498096.
- [6] Wright KD, Hickman R, Laudenslager ML. Hair cortisol analysis: A promising biomarker of HPA activation in older adults. *The Gerontologist*. 2015; 55(Suppl 1): S140-5. doi: 10.1093/geront/gnu174.
- [7] Hellhammer DH, Wust S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*. 2009; 34(2): 163-71. doi: 10.1016/j.psyneuen.2008.10.026
- [8] Inder WJ, Dimeski G, Russell A. Measurement of salivary cortisol in 2012 – laboratory techniques and clinical indications. *Clini Endocrinol*. 2012; 77(5): 645-51. doi: 10.1111/j.1365-2265.2012.04508.x.
- [9] Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry Investig*. 2018; 15(3): 235-45. doi: 10.30773/pi.2017.08.17.
- [10] Kale S, Mane S, Patil P. Wearable biomedical parameter monitoring system: A review. In: 2017 International conference of Electronics, Communication and Aerospace Technology (ICECA) [Internet]. Coimbatore: IEEE; 2017; 614-7 doi:10.1109/ICECA.2017.8203611
- [11] Thapliyal H, Khalus V, Labrado C. Stress detection and management: A survey of wearable smart health devices. *IEEE Consumer Electron Mag*. 2017; 6(4): 64-9. doi:10.1109/MCE.2017.2715578
- [12] Bennett S, Bennett MJ, Chatchawan U, Jenjaiwit P, Pantumethakul R, Kunhasura S, et al. Acute effects of traditional Thai massage on cortisol levels, arterial blood pressure and stress perception in academic stress condition: A single blind randomised controlled trial. *J Bodyw Mov Ther*. 2016; 20(2): 286-92. doi: 10.1016/j.jbmt.2015.10.005
- [13] Sucharit W, Eungpinichpong W, Hunsawong T, Pungsuwan P, Hojo E, Cruz M, et al. Pre- and post-treatment study of the application of a traditional Thai massage protocol for treating office syndrome. *APST*. 2021; 28(3): article ID 28-03-12. doi.org/10.14456/apst.2023.44
- [14] Seo JG, Choi SH, Lee DY. The study of Swedish massage on anxiety situation and PPT. *Medico Legal Update*. 2020; 20(2): 2037-41. doi: 10.37506/v20/i1/2020/mlu/194605
- [15] Mohebb Z, Fazel Dehkordi S, Sharif F, Banitalebi E. The effect of aerobic exercise on occupational stress of female nurses: A controlled clinical trial. *Invest Educ Enferm*. 2019; 37(2): e05. doi: 10.17533/udea.iee.v37n2e05.
- [16] Ayudhaya WSN, Pityaratstian N, Eungpinichpong W, Rattananupong T, Kitidumrongsuk P, Loonlawong S, et al. Effect of behavioral activation on time and frequency domain heart rate variability in older adults with subthreshold depression: a cluster randomized controlled trial in Thailand. *BMC Psychiatry*. 2022; 22(1): 319. doi: 10.1186/s12888-022-03962-8
- [17] Celka P, Charlton PH, Farukh B, Chowienczyk P, Alastruey J. Influence of mental stress on the pulse wave features of photoplethysmograms. *Healthc Techno Lett*. 2020; 7(1): 7-12. doi: 10.1049/htl.2019.0001
- [18] Reece JD, Bunn JA, Choi M, Navalta JW. Assessing heart rate using consumer technology association standards. *Technologies*. 2021; 9(3): 46.
- [19] McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med*. 2012; 22(3): 276-82. PMID: 23092060, PMCID: PMC3900052

- [20] Hajj-Boutros G, Landry-Duval MA, Comtois AS, Gouspillou G, Karelis AD. Wrist-worn devices for the measurement of heart rate and energy expenditure: A validation study for the Apple Watch 6, Polar Vantage V and Fitbit Sense. *Eur J Sport Sci.* 2023; 23(2): 165-77. doi: 10.1080/17461391.2021.2023656.
- [21] Pelaez-Coca MD, Hernando A, Lozano MT, Sanchez C, Izquierdo D, Gil E. Photoplethysmographic waveform and pulse rate variability analysis in hyperbaric environments. *IEEE J Biomed Health Inform.* 2021; 25(5): 1550-60. doi: 10.1109/JBHI.2020.3020743
- [22] Ahn JW, Ku Y, Kim HC. A novel wearable EEG and ECG recording system for stress assessment. *sensors.* 2019; 19(9): 1991. doi.org/10.3390/s19091991
- [23] Sucharit W, Roberts N, Eungpinichpong W, Hunsawong T, Chatchawan U. Standardised 25-step traditional Thai massage (TTM) protocol for treating office syndrome (OS). *IJERPH.* 2023; 20(12): 6159. doi: 10.3390/ijerph 20126159.
- [24] Millstein R. Aerobic Exercise. In: Gellman MD, Turner JR, editors. *Encyclopedia of Behavioral Medicine.* New York, NY: Springer; 2013, p. 48-9. doi.org/10.1007/978-1-4419-1005-9_1087
- [25] Chust-Hernández P, Fernández-García D, López-Martínez L, García-Montañés C, Pérez-Ros P. Female gender and low physical activity are risk factors for academic stress in incoming nursing students. *Perspect Psychiatr Care.* 2022; 58(4): 1281-90. doi: 10.1111/ppc.12928.
- [26] Heijnen S, Hommel B, Kibele A, Colzato LS. Neuro-modulation of aerobic exercise—A review. *Front Psychol.* 2016; 6: 1890. doi: 10.3389/fpsyg.2015.01890.
- [27] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *ACSM.* 2011; 43(7):1 334-59. doi: 10.1249/MSS.0b013e318213febf.
- [28] Suwannakul B, Sangkarit N, Intapunya C, Sompert N, Chantakhat P, Tapanya W. Stress and physical fitness among female university students who regularly exercise during the previous two months. *Arch AHS.* 2023; 35(2): 35-45.
- [29] Chalabianloo N, Can YS, Umair M, Sas C, Ersoy C. Application level performance evaluation of wearable devices for stress classification with explainable AI. *Pervasive and Mobile Computing.* 2022; 87: 101703.

Understanding visual perception skills in autism spectrum disorder: A systematic review

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ABSTRACT

Background: Visual perception in individuals with autism spectrum disorder (ASD) can vary, often showcasing both strengths and challenges. Many individuals with ASD excel in detail-oriented processing, allowing them to focus on fine details rather than the overall picture, which can be advantageous in tasks requiring attention to small details, such as visual search and pattern recognition. Understanding these unique aspects of visual perception in ASD is crucial for developing tailored interventions and support strategies to enhance visual processing abilities and overall social functioning.

Objective: To understand the visual perception skills in autism spectrum disorder.

Materials and methods: The systematic review was registered in PROSPERO and followed the guidelines of PRISMA. A comprehensive search was conducted through the databases (Scopus, PubMed, ProQuest, EBSCOhost, and OTseeker) and printed journals. Studies were included if they focused on visual perception skills in children with autism aged 3-12 years, were peer-reviewed, published between January 2014 and February 2024, and were available in full-text in English. The AXIS Tool for Cross Sectional Studies was used to conduct the critical appraisal.

Results: 19141 studies were derived for database search and 932 from printed journals. A total of sixteen (N=16) studies were identified within the scope of our study. AXIS Tool for Cross-sectional studies was used to evaluate the quality of the sixteen studies. Visual perception skills in ASD have yielded diverse findings, such as perceptual bias, enhanced visual processing, enhanced visual search, and differences in visual processing speed. The review suggested that visual perception impairments are commonly seen in ASD, impacting their functional independence. The review also highlights the importance of understanding the basis of visual perception impairments in this population.

Conclusion: The systematic review concludes that visual perception deficits are one of the primary deficits in autism spectrum disorder. Furthermore, the review reflects on the complex and diverse nature of visual perception skills exhibited by individuals with autism spectrum disorder. These deficits impact overall performance in everyday functioning, especially self-care, academics, and socialization.

Introduction

Autism Spectrum Disorder (ASD) is a pervasive neuro-developmental disorder characterized by persistent deficits in communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities.^{1,2} Visual perception is the brain's ability to receive, process, and interpret visual sensory information a person receives through their eyes.³ Visual perception is broadly categorized into visual receptive and visual cognitive functions. The visual cognitive component

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comprises visual discrimination, a key component of visual cognitive function that can significantly impact an individual's ability to engage in daily activities.⁴ Visual discrimination encompasses objective perception, which involves recognizing specific details of objects, and spatial perception, which refers to understanding the spatial relationship between objects and oneself. Individuals with poor visual closure may struggle to identify objects or symbols when parts are missing, leading to difficulties in tasks such as reading and assembling puzzles.⁴ A lack of depth perception impairs the ability to judge distances, causing challenges in navigating stairs, playing sports, or reaching for objects. Furthermore, deficits in topographical orientation hinder the ability to navigate environments or follow spatial directions, affecting independence in both familiar and unfamiliar settings.⁵ A child might have normal vision yet show deficits in visual perception, impacting functional independence.⁶ Visual perception helps an individual to engage in daily occupations.⁷ For example, activities of daily living (difficulty in putting on shoes/clothes or tying laces, difficulty in using tools), academics (difficulty in reading, writing, and mathematics, difficulty in completing exams on time), play (difficulty in fitting puzzles or parts of toys, difficulty working with block games), and social (negative impact on self-esteem, self-identity). Visual perception develops as the child matures, with most developmental changes taking place and stabilizes by 9 years of age (figure-ground perception by 6-7 years, form constancy by 8-9 years, position in space by 7-9 years, and spatial relationships by 10 years).⁷

Abnormal visual perception is listed as a primary symptom among the behavioral markers observed in early clinical practice of ASD.⁸ The major presentations of abnormal visual perception are visual avoidance, visual exploration, and visual-spatial disorientation.⁹

Children with ASD face difficulties in utilizing visual perception effectively,^{8,9} and exhibit distinct patterns of visual perception compared to those without ASD.¹⁰ Typically, children with ASD concentrate on intricate details, referred to as local structure, while struggling with processing broader, global structures such as the overall picture. Additionally, they often find it challenging to filter out irrelevant visual stimuli in their environment.^{11,12} They demonstrate difficulties in performing daily tasks requiring various visual perception functions such as visual figure-ground, visual form constancy, and visual sequencing memory abilities.¹³

Studies have proposed that heightened perceptual abilities, preferences for processing local details, and intense states of focus are connected conceptually to the restricted and repetitive behavior (RRB) symptoms, particularly selective interests and resistance to shifting attention.^{14,15} Visual perception in ASD is also linked to sensory sensitivity. Some individuals with ASD may experience heightened sensitivity to visual stimuli, leading to sensory overload or difficulties processing visual information in complex environments.¹⁶ Abnormal visual perception in ASD impacts their school performance (handwriting, reading, fixation with objects, and

maintaining eye contact) and social participation. Abnormal visual perception in children with ASD has a significant impact on various aspects of their daily functioning. Studies have shown that deficits in visual perception, such as difficulties with visual discrimination, figure-ground perception, and visual memory, can hinder essential skills like self-care, social interaction, and academic performance.¹⁷ Poor visual perception abilities are also linked to challenges in processing facial recognition and understanding social cues, which can further exacerbate social communication difficulties in children with ASD.¹⁸ Additionally, impaired motion processing, as part of abnormal visual perception, can affect how children navigate their environment and interact with moving objects, impacting their ability to perform daily tasks.¹⁹ These deficits, when unaddressed, contribute to the broader functional limitations observed in children with autism.²⁰

Occupational therapy (OT) professionals play a crucial role in improving visual perception deficits in children with ASD, which can impact their ability to perform daily tasks, including reading, writing, and engaging in social interactions.²¹ Occupational therapists use evidence-based interventions, such as visual-motor integration activities, sensory integration therapy, and environmental modifications, to enhance the child's ability to process visual information. These interventions target core visual perception skills like figure-ground discrimination, spatial relations, and visual-motor coordination, essential for tasks like copying shapes, identifying objects, and navigating spaces. Through structured therapy sessions, children are supported in developing these skills in a way that promotes greater independence and participation in daily life activities.²¹

OT interventions can significantly improve visual perception abilities in children with ASD, leading to better functional outcomes. For example, a study²¹ demonstrated that sensory-based occupational therapy, including activities designed to enhance visual processing, improved attention, behavior, and task performance in children with ASD. Another study emphasized the benefits of occupational therapy interventions incorporating sensory integration techniques, noting improvements in visual-motor skills and overall functional performance.²² Both studies underscore the effectiveness of OT interventions in improving functional outcomes in children with ASD, particularly in enhancing visual processing and behavior. The previous study examined the role of sensory-based occupational therapy in improving classroom behaviors and educational outcomes.²¹ The study demonstrated that children who received sensory-based OT interventions improved attention, emotional regulation, and task performance in classroom settings, with enhanced visual processing playing a pivotal role in these outcomes. Similarly, the latter focused on the efficacy of the Get Ready to Learn yoga program, a sensory integration-based OT intervention and found improvements in visual-motor skills, behavior, and overall task performance.²² In both studies, the interventions led to better engagement,

attention, and functional performance, supporting that OT interventions targeting sensory and visual processing deficits can yield positive functional outcomes for children with ASD.

This unique nature of visual perception skills exhibited by children with ASD highlights the need for a thorough systematic review. Understanding these nuances is crucial for developing targeted interventions and support strategies that address the specific visual perceptual needs of individuals with ASD.

This systematic review aims to understand the visual perception skills in autism spectrum disorder.

The scope of this review was to systematically analyze studies focusing on visual perception skills in children with autism spectrum disorder (ASD) aged 3-12 years. It aimed to explore strengths and deficits in visual perception across various domains, such as visual memory, discrimination, and spatial relationships, and examine how these skills impact functional areas like self-care, socialization, and academic performance. The review also assessed the methodologies used in these studies, including standardized and non-standardized assessments, while identifying gaps for future research, particularly in dynamic visual perception.

Materials and methods

This systematic review was conducted using the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO with the ID CRD42024547616. PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and global development, where there is a health-related outcome. It aims to provide a comprehensive listing of systematic reviews registered at inception to help avoid duplication. The Center produces it for Reviews and Dissemination, University of York, York, United Kingdom, and funded by the National Institute for Health Research (NIHR).

Search procedure

A comprehensive search of studies was conducted using electronic databases, namely, Scopus, PubMed, ProQuest, EBSCOhost, and OTseeker. Additionally, studies were also searched from printed journals [American Journal of Occupational Therapy (AJOT), British Journal of Occupational Therapy (BJOT), Canadian Journal of Occupational Therapy (CJOT), Indian Journal of Occupational Therapy (IJOT), and Journal of Autism and Developmental Disabilities (JADD)].

Search strategy

The search strategy used MeSH terms and “OR” and “AND” Boolean operations.

MeSH terms	Search strategy
Visual perception	“visual perception” OR “visual perceptual” OR “vision” OR “visual perception skills” OR “visual perceptual skills” OR “visual processing” OR “global local processing” OR “visual discrimination” OR “visual motion perception” OR “visual figure ground” OR “visual form constancy” OR “visual search” OR “visual motor integration” OR “visual attention” OR “visual memory” OR “visual spatial relationships”
AND	
autism	“autism” OR “autism spectrum disorder” OR “autistic disorder” OR “aspergers syndrome” OR “pervasive developmental disorder”
Database/Journal	Database query
ProQuest AJOT BJOT CJOT JADD OTseeker IJOT	“visual perception” OR “visual perceptual” OR “vision” OR “visual perception skills” OR “visual perceptual skills” OR “visual processing” OR “global local processing” OR “visual discrimination” OR “visual motion perception” OR “visual figure ground” OR “visual form constancy” OR “visual search” OR “visual motor integration” OR “visual attention” OR “visual memory” OR “visual spatial relationships” AND “autism” OR “autism spectrum disorder” OR “autistic disorder” OR “aspergers syndrome” OR “pervasive developmental disorder”
PubMed	“visual perception” OR “visual perceptual” OR “vision” OR “visual perception skills” OR “visual perceptual skills” OR “visual processing” OR “global local processing” OR “visual discrimination” OR “visual motion perception” OR “visual figure ground” - Search Results - PubMed (nih.gov)
Scopus	“visual perception” OR “visual perceptual” OR “vision” OR “visual perception skills” OR “visual perceptual skills” OR “visual processing” OR “global local processing” OR “visual discrimination” OR “visual motion perception” OR “visual figure ground” OR “visual form constancy” OR “visual search” OR “visual motor integration” OR “visual attention” OR “visual memory” OR “visual spatial relationships” AND “autism” OR “autism spectrum disorder” OR “autistic disorder” OR “aspergers syndrome” OR “pervasive developmental disorder” AND PUBYEAR > 2013 AND PUBYEAR < 2025 AND (LIMIT-TO (SUBJAREA, “MEDI”) OR LIMIT-TO (SUBJAREA, “NEUR”) OR LIMIT-TO (SUBJAREA, “PSYC”) OR LIMIT-TO (SUBJAREA, “SOCI”) OR LIMIT-TO (SUBJAREA, “HEAL”) OR LIMIT-TO (SUBJAREA, “MULT”) AND LIMIT-TO (DOCTYPE, “ar”) AND LIMIT-TO (LANGUAGE, “English”) AND LIMIT-TO (SRCTYPE, “j”) OR LIMIT-TO (SRCTYPE, “p”) AND LIMIT-TO (PUBSTAGE, “final”) AND LIMIT-TO (OA, “all”)

Data extraction and data analysis

The search results were downloaded with all titles and abstracts from electronic databases in Microsoft Excel (CSV file). Two principal authors initially reviewed the titles and focused on the initial screening of the articles based on the search strategy derived. Following the title screening, abstracts of the articles were read and screened thoroughly to determine if they met the criteria for inclusion. In cases where there were disparities in opinions between the two authors regarding particular articles or when articles did not align with the inclusion criteria, an independent reviewer re-assessed them to validate the decision to exclude them. Disagreements between reviewers in selecting studies were typically resolved through a consensus process. When reviewers encountered discrepancies in study inclusion or exclusion, they engaged in discussions to review the criteria and the reasons for their differing opinions. If consensus could not be reached through discussion, an independent reviewer was often consulted to make a final decision based on the established inclusion criteria. This process ensured that the review remained rigorous and that all decisions were based on a thorough evaluation of the evidence. After the full-text review, the two primary authors independently scored the articles using the AXIS (Appraisal tool for Cross-Sectional Studies).²³ In case of disagreements or inconsistencies between the two authors' scores, all the authors reached a consensus on the final scores.

The AXIS (Appraisal Tool for Cross-Sectional Studies). Tool, comprising 20 elements with three possible answers (Yes, No, and Don't Know), was utilized to evaluate the risk of bias.²³ Two authors independently assessed the included studies' quality, resolving disagreements through consensus.

This collaborative process ensured that the review was accurate and reliable. Data was extracted based on the demographic characteristics and measures used to assess visual perception and visual perception profile of children with autism.

Inclusion and exclusion criteria

Studies were included if (1) they focused on visual perception skills in autism; (2) on children aged 3-12 years; (3) they were published between the years January 2014 and February 2024; (4) they were available in English; (5) peer-reviewed studies; (6) available in full-text. Systematic reviews, meta-analyses, case series, case reports, and expert opinions were excluded from the study.

Results

A total of 20073 records were identified through search, among which 19141 were screened through database screening and 932 records through journal search. 19813 records were identified after removing duplicates (N=260), and 19813 were screened for title and abstract screening. Thirty-one studies were included after title screening, and twenty were included after abstract screening. Studies were excluded as they did not focus on the age group selected for the present review, did not focus on children with autism, non-original articles (reviews, commercials, editorials, and opinions), and if the study was not available in the English language. A total of sixteen (N=16) studies were included for full-text review based on the scope of the current study. Figure 1 depicts the flowchart of the records screening process. Table 1 describes the detailed outline of records screened through database and journal screening. Table 2 illustrates the visual perception profile of ASD based on the included studies.

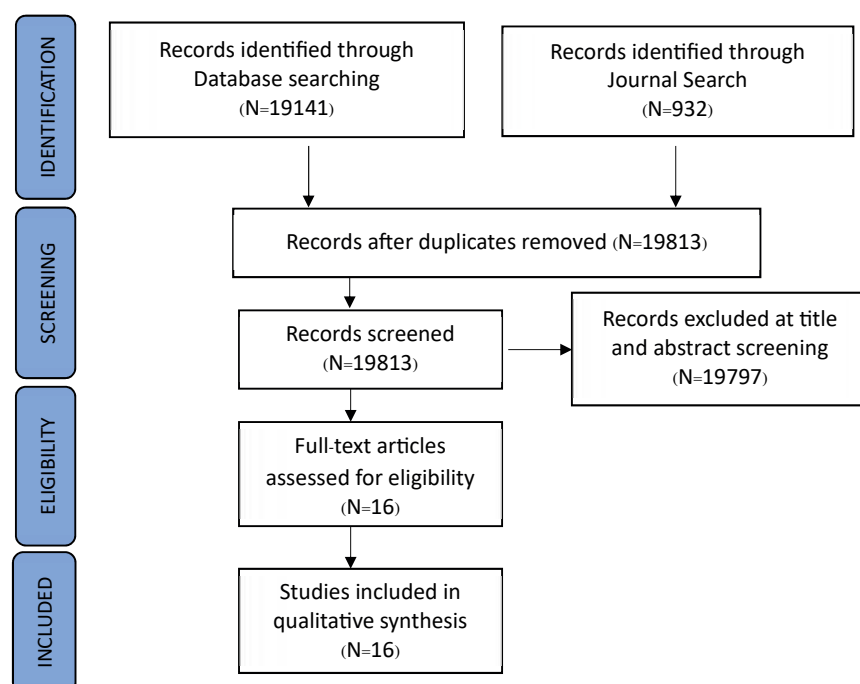


Figure 1. PRISMA flow diagram.

Table 1. Screening of records obtained from database and journal screening.

Database/journals	Total search	On title screening	On abstract screening	On full-text screening
Database screening				
ProQuest	3216	5	2	2
PubMed	928	8	8	8
Scopus	14318	12	10	6
OTseeker	286	0	0	0
EBSCOhost	393	0	0	0
Journal screening				
IJOT	9	0	0	0
AJOT	296	2	0	0
JADD	321	4	0	0
BJOT	190	0	0	0
CJOT	116	0	0	0

Table 2. Visual perception skills in ASD.

Year/Author	Level of evidence	Research design	Study purpose	Study participants(sample size, selection criteria, ASD screening)	Visual perception assessment	Result summary
Vetrayan J et al. ²⁹	IV	Cross sectional study	To investigate the significant relationship between visual perception and imitation in school functioning among children with ASD.	N=20, 4-9.6 years school going, diagnosed on DSM IV and CARS, have sufficient cognition skills to follow simple commands and instructions during tests, IQ on mild to moderate level on Stanford Binet Intelligence Scale	DTVP-2	The result revealed that school function of autistic children has a significant relationship with their visual perception and imitation performance. Especially the Motor-reduced Visual Perception subtest, unstructured gesture & object imitation
Hallen RV et al. ²⁷	IV	Cross sectional study	To study two visual search paradigms featuring Gaborized stimuli to evaluate the effects of task distractors and task instructions on local-global visual processing in children with ASD and TDC.	Expt. 1: 6-10 years, Dutch-speaking children, with normal or corrected-to-normal vision, N=21 diagnosed with ASD on DSM-IV-TR and ADOS-2 Expt. 2: 8-14 years, Dutch-speaking children, with normal or corrected-to-normal vision, N=26 diagnosed with ASD on DSM-IV-TR	Visual search tasks (Gaborized stimuli and local-global visual processing)	ASD did not show improved performance for the visual search tasks. Furthermore, no significant differences in their sensitivity to local versus global aspects of visual stimuli were observed.
Brown A C & Crewther DP ³⁹	IV	Cross sectional study	To address the inspection times (ITs) for novel global/local stimuli and recording nonlinear visually evoked potentials, specifically focusing on the magnocellular and parvocellular temporal efficiencies.	N=11, 7-11 years, male ASD recruited from primary school, diagnosed on DSM IV	Inspection time test	ASD exhibited Slower inspection time
Cherenkova L V et al. ³⁸	IV	Cross sectional study	To compare the role of various levels of magno-parvocellular channels in processing visual information and their influence on the development of cognitive and speech processes in children with typical and atypical development.	N=58 (N=19 ASD diagnosed on CARS), children pre-school department of primary school-kindergarten, right-handed, no problems with vision and hearing	Task for contrast sensitivity, global motion threshold	Deficit of global motion thresholds based on stationary object orientation was found only in ASD cases; manifestation of such deficit depended on the autistic disorder severity. In mild ASD cases, figure recognition time increased only with increasing number of locations of targets among demonstrated figures. Children with severe ASD demonstrated constant increase in detection time.

Table 2. Visual perception skills in ASD (continued).

Year/Author	Level of evidence	Research design	Study purpose	Study participants(sample size, selection criteria, ASD screening)	Visual perception assessment	Result summary
DiCriscio A S and Troiani V ³⁰	IV	Cross sectional study	To examine the relationship between individual differences in visual processing skills and quantitative measures of autism traits exhibiting a range of clinical features.	N=54, 5-16 years Diagnosed with autism traits, with an IQ of ≥ 69	TVPS-3	BAPQ significantly predicted figure ground subtest Linear relationship exists between figure ground and autism traits.
Jobs E N et al. ³⁴	IV	Cross sectional study	To assess Local and Global Visual Processing in 3-Year-Olds with and without ASD	N=49, 3 years old Diagnosed on DSM 5 criteria, ADOS 2, ADI-R, VABS-II, parental checklist	<i>Local Measures:</i> Children's Embedded Figures Test, Figure Ground Task, Hidden Pictures <i>Global Measures:</i> The Fragmented Picture Test, Gestalt Closure	Enhanced performance on the local task Hidden Pictures differentiated children with ASD from the other groups.
Gunal A et al. ²⁵	IV	Cross sectional study	To compare the motor and cognitive skills of children with autism to those of their typically developing peers, as well as to examine how motor and cognitive difficulties impact daily living activities and the quality of life of these children.	N=30 TDC and N=32, aged 6-12 years, diagnosed with autism on DSM-IV-TR, attending a special school, with IQ >70	LOTCA (Subtests: Orientation, Perception, Visual Perception, Thinking operations)	Children with ASD obtained lower scores than TD in perception, and visual perception domain, these deficits were further correlated with self-care and social functions.
Guy J et al. ²⁸	IV	Cross sectional study	To explore how global and local processes vary with age, while not explicitly separating the effects of interference in ASD	N=83 (N=39 ASD and N=41 TDC), diagnosed as ASD on ADOS and/or ADI-R, DSM IV (only individuals diagnosed as autistic disorder (not Asperger's), 6 -16 years	Navon task	Children and adolescents with ASD exhibit slower responses to global information compared to TD peers when there is no interference. However, when interference is present, individuals with ASD tend to show a more significant impact of local information on global processing. The reaction time trajectories in global and local conditions were compared between both groups.

Table 2. Visual perception skills in ASD (continued).

Year/Author	Level of evidence	Research design	Study purpose	Study participants(sample size, selection criteria, ASD screening)	Visual perception assessment	Result summary
Rose S A et al. ³⁷	IV	Cross sectional study	To explore selective attention in Rett syndrome, a profoundly disabling neurodevelopmental disorder resulting from mutations in the X-linked MECP2 gene.	N=28 females with Rett syndrome and N=32 age-matched typically developing children, 2-12 years Diagnosed on the Rett Syndrome Severity Scale	Search task with eye-tracking technology	Selective attention, the ability to focus on or select a particular element or object in the environment, is compromised by Rett syndrome.
Seernani D et al. ³⁶	IV	Cross sectional study	To thoroughly examine the execution of a visual search task in both typical and clinical groups (ASD, ADHD)	N=100 (ASD without comorbidities N=15, ASD with comorbidities N=18), diagnosed on ADOS, ADI-R	Visual search task	ASD+ group was particularly slow, inefficient, and had significantly longer fixations, absence of superior search
Chi I J et al. ²⁶	IV	Cross sectional study	To study the relationship between self-care and visual perception in young children with ASD.	N=132 (N=66 ASD, N=66 TDC), diagnosed on DSM 5 and CARS2-ST, aged 48-83 months	DTVP-3 TVPS-3	ASD obtained significantly lower scores for self-care performance and visual perception ability compared with TDC. Positive correlations were found between self-care performance and visual perception ability in ASD.
Wuang Y P et al. ³¹	IV	Cross sectional study	To explore sensory integration and perceptual-motor skills in elementary school children (ages 5 to 12) with ASD in Taiwan.	N=117, 5-13 years, no serious physical or behavioral problems, diagnosed with autism	TVPS-3	The ASD participants had best performance on the visual spatial relationship, but it was still in the impaired range. The participants had significant impairments on performing form constancy, figure ground and visual closure tasks.
DiCriscio A S and Troiani V ³²	IV	Cross sectional study	to evaluate significant differences in visual-perceptual skills among children with and without ASD using TVPS	N=87 (N=48 ASD), 5-16 years Diagnosed on DSM 5	TVPS-3	A significant linear relationship between ASD features and performance on the TVPS Figure Ground subtest.
Liu C et al. ²⁴	IV	Cross sectional study	To explore the line bisection tasks in children with ASD by assessing the impacts of line length, hand use, and line end cues through two distinct experiments.	N=31 diagnosed as ASD, 5-15 years, right-handed, passed a comprehensive check, normal or corrected-to-normal visual acuity & ability to concentrate on a task for at least 15 minutes, not on antipsychotic medicine; N=20 TDC	Manual line bisection task	ASD and TD individuals show a similar preference for processing visual information on the left side. However, when asked to use their left hands to divide short lines, ASD might display a different or unusual bias pattern.

Table 2. Visual perception skills in ASD (continued).

Year/Author	Level of evidence	Research design	Study purpose	Study participants (sample size, selection criteria, ASD screening)	Visual perception assessment	Result summary
Faber L et al. ³³	IV	Cross sectional study	To assess and associate the motor skills, visual perception, and visual-motor integration = of children and youth with ASD in comparison to age- and gender-matched peers without ASD.	N= 67 ASD and 54 non-ASD, grade 4 to grade 9 Diagnosed as ASD on DSM 5 and autism, Asperger's or PDD-NOS on DSM IV	Beery VMI 6 (Main test and supplemental test of visual perception)	No significant differences were found between children and youth with and without ASD for VP or VMI as measured with the Beery VMI-6. Children and youth with ASD perform similar to children and youth without ASD for VP and VMI (as measured with the Beery-VMI-6).
Lin LY et al., ³⁵	IV	Cross sectional study	To study the influence of motor-free visual perception on the connection between self-care and visual-motor integration in young children with ASD.	N=66 young children with ASD, aged 48-83 months old from Tainan, diagnosed on DSM 5 criteria and CARS, IQ ranging from 67-127	DTVP-3 TVPS-3	Self-care skills were strongly linked to abilities like visual-motor integration, visual discrimination, visual memory, and understanding visual spatial relationships. Among these, visual sequential memory and understanding spatial relationships were the most crucial factors influencing self-care skills. Sequential memory played a role in how well visual-motor integration affected self-care abilities.

Note: LOTCA: Lowenstein Occupational Therapy Cognitive Assessment, TDC: Typically developing children, ASD: Autism Spectrum Disorder, AD/ID: Attention Deficit Hyperactivity Disorder, IQ: Intelligence Quotient, DTVP 3: Developmental test of Visual Perception: Third Edition, TVPS 3: Test of Visual Perception Skills: Third Edition; ADOS 2: Autism Diagnostic Observation Scale: Second Edition, ADI-R: Autism Diagnostic Inventory: revised; Beery VMI 6: Beery Buktenica Developmental Test of Visual Motor Integration: Sixth Edition, DSM: Diagnostic and Statistical Manual, CARS: Childhood Autism Rating Scale.

In this synthesis, the methodological quality of the sixteen cross-sectional studies included in the systematic review was evaluated using the AXIS tool. For 3 out of the 20 questions pertaining to statistical significance, the description of statistical methods, and the explanation of analysis studies received a “Yes” response, indicating a low risk of bias in these areas. However, for questions regarding sample size justification and non-response bias, the responses were either “No” reflecting a moderate to severe risk of bias in all studies. For the remaining questions, most studies demonstrated a low risk of bias.

All 16 studies were cross-sectional; none were longitudinal or randomized controlled trials. The 16 studies collectively highlight various findings related to visual perception and its association with self-care skills and cognitive functioning in children and adolescents with ASD. Visual perception impairments in ASD children affect cognitive and functional domains, including self-care and school performance. Local Bias is a hallmark of visual processing in ASD, with ASD participants showing better performance on local tasks but impaired global processing. Sequential Memory and Spatial Relationships are key visual-motor integration abilities that influence self-care skills. Visual processing deficits in ASD are further complicated by the severity of autism traits, which have a direct influence on performance in tasks like figure-ground perception. Despite impairments, in some areas like visual-motor integration, children with ASD perform similarly to TD peers, highlighting the complexity of visual perception and cognitive processing in ASD.

Key findings from the included studies

All 16 studies indicated impairments in visual perception in ASD. Children with ASD often show deficits in visual discrimination, figure-ground perception, visual memory, and visual-motor integration compared to typically developing (TD) peers. These deficits are linked to slower processing times, especially when processing global information, leading to difficulties in tasks requiring higher-order visual perception skills. Studies consistently found that impairments in visual perception are strongly related to problems in daily living skills, such as self-care and social functioning. Some studies suggest that while children with ASD exhibit deficits in global visual processing, they may excel in tasks requiring local visual processing, such as recognizing specific details or patterns. Although most studies suggest visual discrimination is impaired, a few findings indicate that children with ASD may show strengths in particular aspects of visual discrimination, depending on the assessment tools used and task complexity. These mixed results suggest variability in the visual perception profile of children with ASD. The studies predominantly assessed static visual perception tasks, neglecting the dynamic aspects (e.g., processing moving objects), which are crucial for navigating real-life environments. The need to determine both static and dynamic visual perception to understand the deficits in ASD was emphasized fully.

Discussion

The systematic review reflects on the complex and diverse nature of visual perception skills exhibited by children with autism spectrum disorder aged 3-12 years. While some studies suggest that visual perception is a deficit in children with ASD, characterized by impairments in tasks such as figure-ground discrimination, visual memory, and form constancy, others propose that visual perception can be a relative strength in specific areas. For instance, children with ASD often excel in tasks focusing on fine details or local visual information. This notion is supported by theoretical foundations related to ASD, i.e., enhanced perceptual functioning (EPF) and the weak central coherence (WCC) theory, which suggest that children with autism have deficits in visual perception due to the slower processing of visual input in the later stages.^{13,15,16} Additionally, visual perception deficits in autism are hypothesized to be related to developmental abnormalities that occur during early life, resulting in rapid extension of the visual cortex surface area. This causes abnormal transmission of visual evoked potential.^{40, 41}

When assessing visual perception skills in ASD, age and gender were found to be independent factors among the included studies. However, the complexity of stimuli significantly impacted the performance of children with ASD, placing a high cognitive demand on them and leading to severe impairment in their performance of visual perception.

Visual perception profile

Children with ASD demonstrated strong performance but in an impaired range in the spatial relationships domain.³¹ This might be due to the insufficient visual-spatial processing abilities affecting the mirror neuron system and subsequently impacting imitation skills in ASD.⁴⁰

Visual discrimination skills in children with ASD show contrasting findings across studies. Some studies propose that ASD individuals focus more on detailed parts than global parts due to their discrete attention strategy. Theories like Weak Central Coherence and Enhanced Perceptual Functioning support this perspective.^{12,14,15} However, there are also studies presenting the opposite view.²³ These discrepancies could stem from demographic variations, cultural factors, and the specific measures used to assess this ability.

Figure-ground perception in autism has produced conflicting results. One study¹⁶ suggests reduced global processing abilities, while others argue the opposite. These differences stem from variations in search strategies, such as serial search, employed by individuals with autism spectrum disorder (ASD) when locating stimuli. The choice of search strategy in ASD individuals appears to be influenced by their social impairments and individual differences¹⁶.

Visual memory and visual sequential memory deficits are also seen in autistic children. This may be due to the difficulty in information processing and processing rapid visual stimuli.³⁷ Additionally, children with autism reported

having difficulty processing facial recognition as compared to object memory.⁴¹

Children with ASD also exhibit impairments in form constancy and visual closure abilities, which are closely tied to their visual discrimination and mental rotation skills.⁴⁰ Mental rotation involves the coordination of both the dorsal and ventral visual processing streams. Studies have shown that children with ASD have altered neural activity in the prefrontal cortex network, contributing to these challenges in mental rotation tasks and overall visual perception.⁴²

Impact of visual perception skills on performance areas

A study concluded that the perception subset (visual identification of objects, overlapping figures, space position, praxis) and visual perception subset (reproduction of a two-dimensional model, puzzle, drawing a clock) of LOTCA were strongly related to the self-care skills and social function of PEDI.³⁵ Similar results were found in a study,³¹ which stated that children with ASD performed significantly worse on communication, socialization, and daily living skills. Another study revealed that motor-reduced visual perception skills are strong contributors to school functioning (travel, maintaining and changing positions, recreational movement, manipulation with movement, using materials, setup and cleaning, eating and drinking, hygiene, clothing management, functional communication, task behavior/completion, positive interaction, and personal care awareness).²⁹ A study revealed a significant relationship between self-care and visual perception domains.²⁶ Another study revealed that visual sequential memory and visual-spatial relationships were the primary factors influencing self-care performance.³⁵ Sequential memory played a mediating role in the connection between visual-motor integration and self-care performance.

Impairments in visual perception skills significantly impact various aspects of functioning, including self-care, socialization, and school performance, among children with autism.^{25,26,31,32} Studies have shown that children with autism heavily rely on visual instructions, enabling them to imitate and replicate tasks, thus highlighting the crucial role of visual perception abilities in their academic success.³⁴ Moreover, visual perception plays a vital role in learning and executing self-care activities, as children with autism often utilize visual strategies for these tasks.⁴⁴ The interrelation between visual perception and socio-cognitive deficits in autism is noted, with both aspects being linked to the superior temporal sulcus (STS).¹²

Assessment of visual perception

Among the measures used to assess visual perception, the Test of Visual Perception Skills-Third Edition (TVPS-3) was used in most studies. TVPS-3 has good internal consistency, test-retest reliability, and good criterion-related validity.⁴⁵ It has been used to evaluate the visual perceptual skills of children with different ranges of autism traits.¹⁶ On the contrary, using various non-standardized methods to evaluate visual perception

reduces the reliability of the assessment due to the absence of established psychometric properties.

Studies on visual perception in autism often focus on static constructs, neglecting the crucial aspect of integrating space and objects in motion, which is essential in real-life scenarios.¹² Children with ASD commonly experience impaired motion processing due to dysfunction in the dorsal stream of visual processing.^{12,46} However, most studies reviewed here primarily assess static visual perception constructs, overlooking this dynamic component critical for understanding how these children navigate their environment and interact with moving objects. The study's major limitation was that only studies published in English were included in the systematic review.

Future scope and recommendations

To enhance the utility of the review for practitioners and policymakers, future research should focus on using standardized, validated assessment tools to ensure consistency and reliability in measuring visual perception skills. Incorporating dynamic visual tasks that simulate real-life scenarios will provide a more comprehensive understanding of how children with ASD interact with their environment. Implementing blinding techniques to minimize bias and conducting longitudinal studies to track the development of visual perception skills over time is also crucial. Developing and evaluating tailored interventions for specific visual perception deficits will also improve therapeutic and educational practices. Including studies from diverse cultural backgrounds will ensure findings are broadly applicable and culturally relevant. Lastly, fostering interdisciplinary collaboration among researchers, clinicians, and educators will integrate insights from various fields, leading to more effective approaches for addressing visual perception deficits and enhancing functional outcomes for children with ASD.

Strengths of the systematic review

The systematic review comprehensively analyzes visual perception deficits in children with autism spectrum disorder (ASD). The review explores various subdomains of visual perception challenges in ASD, such as visual discrimination, figure-ground perception, and visual memory, providing valuable insights into their diversity. It emphasizes the importance of using validated assessment tools, like the Test of Visual Perception Skills-Third Edition (TVPS-3), in clinical settings. The recommendation for standardized, evidence-based practices in assessing and treating visual perception deficits contributes to more effective interventions tailored to the unique needs of children with ASD.

Limitations

The review only included studies published in English. Most of the included studies used a cross-sectional design, which limits the ability to conclude the developmental trajectory of visual perception skills over time in children with ASD.

Conclusion

The systematic review concludes that visual perception skills are one of the crucial factors deficient in children with ASD. The range of visual perception deficits in ASD is diverse and evident, impacting their functional performance. Future studies are warranted to assess both static and dynamic domains of visual perception. Additionally, longitudinal studies are essential to explore the developmental trajectory of visual perception skills in children with ASD.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th Ed). American Psychiatric Publishing, Inc. doi.org/10.1176/appi.books.9780890425596.
- [2] World Health Organisation. (2019). Autism spectrum disorders-fact sheets. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorder>.
- [3] Brown T. Validity and reliability of the Developmental Test of Visual Perception- third edition (DTVP-3). Occupational Therapy in Health Care 2016; 30(3): 272-87. <https://doi.org/10.3109/07380577.2015.1136757>.
- [4] Schneck CM. A frame of reference for visual perception. Frames of Reference for Pediatric Occupational Therapy: Third Edition. Lippincott Williams & Wilkins, 2010. P. 349-86.
- [5] Solomon JW, O'Brien JC. Pediatric Skills for Occupational Therapy Assistants. 5th Ed. Mosby, 2020.
- [6] Peheré NK, Dutton GN. Perceptual visual dysfunction in children - An Indian perspective. Indian J Ophthalmol. 2021; 69(8): 2004-11. doi:10.4103/ijo.IJO_1996_20.
- [7] Schneck CM. Visual Perception. In: Case-Smith J, O'Brien JC. Occupational Therapy for Children, Sixth Edition. Missouri: Mosby Elsevier; 2010.
- [8] Zwaigenbaum L, Bauman ML, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Choueiri R, Fein D, Kasari C, Pierce K, Buie T, Carter A, Davis PA, Granpeesheh D, Mailloux Z, Newschaffer C, Robins D, Roley SS, Wagner S, Wetherby A. Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research. Pediatr. 2015; 136(Suppl 1): S10-40. doi:10.1542/peds.2014-3667C.
- [9] Apicella F, Costanzo V, Purpura G. Are early visual behavior impairments involved in the onset of autism spectrum disorders? Insights for early diagnosis and intervention. Eur J Pediatr. 2020; 179: 225-34; <https://doi.org/10.1007/s00431-019-03562-x>.
- [10] Lidstone DE, Mostofsky S H. Moving toward understanding autism: Visual-motor integration, imitation, and social skill development. Pediatr Neurol. 2021;122: 98-105. doi.org/10.1016/j.pediatr.neurol.2021.06.010.
- [11] Schriber Orloff SNS. Learning disability in plain English. In Learning re-enabled (p. 5-17). doi.org/10.1016/b978-0-323-02772-4.50007-x.
- [12] Dakin S, Frith U. Vagaries of visual perception in autism. Neuron. 2005; 48(3): 497-507. doi.org/10.1016/j.neuron.2005.10.018.
- [13] Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P, Pollick FE. Vision in autism spectrum disorders. Vis Res. 2009; 49: 2705-39. doi:10.1016/j.visres.2009.08.005.
- [14] Happé F, Briskman J, Frith U. Exploring the cognitive phenotype of autism: Weak "Central Coherence" in parents and siblings of children with autism: I. Experimental tests. J Child Psychol Psychiatry. 2001; 42(3): 299-307. doi.org/10.1111/1469-7610.00723.
- [15] Happé F G, Booth R D. The power of the positive: Revisiting weak coherence in autism spectrum disorders. Q J Exp Psychol (Hove). 2008; 61(1): 50-63.
- [16] Sabatino DiCrisio A, Troiani V. The Broader Autism Phenotype and Visual Perception in Children. J Autism Dev Disord. 2018; 48(8): 2809-20. doi:10.1007/s10803018-3534-9.
- [17] Smith J, Brown A, Miller C. Impact of visual perception deficits on daily functioning in children with Autism Spectrum Disorder. J Autism Dev Disord. 2019; 49(3): 458-70.
- [18] Johnson PL, Green S. Visual perception challenges in children with ASD: Implications for social interaction and communication. Autism Res. 2020; 13(5): 655-68.
- [19] Brown A, Miller C. Motion processing deficits and environmental navigation in children with Autism Spectrum Disorder. Dev Neuropsychol. 2021; 46(2): 122-35.
- [20] Davis R, Smith J, Lee H. The role of visual perception in functional limitations among children with ASD. J Pediatr Neuropsychol. 2018; 14(2): 212-24.
- [21] Ashburner J, Ziviani J, Rodger S. Sensory processing and classroom emotional, behavioral, and educational outcomes in children with autism spectrum disorder. AJOT. 2014; 68(5): 562-73. doi.org/10.5014/ajot.2014.011221.
- [22] Koenig KP, Buckley-Reen A, Garg S. Efficacy of the Get Ready to Learn yoga program among children with autism spectrum disorders: A pretest-posttest control group design. American Journal of Occupational Therapy. 2012; 66(5): 538-46. doi.org/10.5014/ajot.2012.004390.
- [23] Downes MJ, Brennan ML, Williams HC, et al. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS)BMJ Open. 2016; 6: e011458.
- [24] Liu C, Zhai H, Su S. et al. Visuospatial Bias in Children with Autism Spectrum Disorder: Evidence from Line Bisection Tasks. J Autism Dev Disord. 2022;52: 4861-71. doi.org/10.1007/s10803-021-05350-9.
- [25] Ayla Günal, Gonca Bumin & Meral Huri. The Effects

- of Motor and Cognitive Impairments on Daily Living Activities and Quality of Life in Children with Autism. *J Occup Ther Sch Early Interv.* 2019; 12: 444-54. doi:10.1080/19411243.2019.1604286.
- [26] Chi IJ, Lin LY. Relationship Between the Performance of Self-Care and Visual Perception Among Young Children With Autism Spectrum Disorder and Typical Developing Children. *Autism Res.* 2021; 14: 315-23. doi:10.1002/aur.2367.
- [27] Van der Hallen R, Evers K, Boets B, Steyaert J, Noens I, Wagemans J. Visual Search in ASD: Instructed Versus Spontaneous Local and Global Processing. *J Autism Dev Disord.* 2016; 46: 3023-36. doi:10.1007/s10803-016-2826-1.
- [28] Guy J, Motttron L, Berthiaume C, Bertone A. A Developmental Perspective of Global and Local Visual Perception in Autism Spectrum Disorder. *J Autism Dev Disord.* 2019;49: 2706-20. doi:10.1007/s10803-016-2834-1.
- [29] Vetrayan J, Zin MFM, Paulraj SJP. Relationship between visual perception and imitation in school function among autism. *Procedia Soc Behav Sci.* 2015; 202: 67-75. doi.org/10.1016/j.sbspro.2015.08.209.
- [30] Sabatino DiCriscio A, Troiani V. The broader autism phenotype and visual perception in children. *J Autism Dev Disord.* 2018; 48: 2809-20. doi:10.1007/s10803-018-3534-9.
- [31] Wuang YP, Huang CL, Tsai HY. Sensory Integration and perceptual-motor profiles in school-aged children with autistic spectrum disorder. *Neuropsychiatr Dis Treat.* 2020; 6: 1661-73. doi:10.2147/NDT.S253337.
- [32] DiCriscio AS, Smith J, Troiani V. Comprehensive assessment of visual perceptual skills in autism spectrum disorder. *Front Psychol.* 2021; 13: 662808. doi:10.3389/fpsyg.2021.662808.
- [33] Faber L, van den Bos N, Houwen S, Schoemaker M M, Rosenblum S. Motor skills, visual perception, and visual-motor integration in children and youth with Autism Spectrum Disorder. *Res Autism Spectrum Dis.* 2022; 96:101998. doi.org/10.1016/j.rasd.2022.101998.
- [34] Nilsson Jobs, E, Falck-Ytter, T, Bölte, S. Local and global visual processing in 3-year-olds with and without autism. *J Autism Dev Disord.* 2018; 48: 2249-57. doi.org/10.1007/s10803-018-3470-8.
- [35] Lin LY, Chi IJ, Sung YS. Mediating effect of sequential memory on the relationship between visual-motor integration and self-care performance in young children with autism spectrum disorder. *Front Psychol.* 2022; 13: 988493. doi:10.3389/fpsyg.2022.988493.
- [36] Seernani D, Damania K, Ioannou C, Penkalla N, Hill H, Foulsham T, Kingstone A, Anderson N, Boccignone G, Bender S, Smyrnis N, Biscaldi M, Ebner-Priemer U, Klein C. Visual search in ADHD, ASD and ASD + ADHD: overlapping or dissociating disorders? *Eur Child Adolesc Psychiatry.* 2021; 30: 549-62. doi:10.1007/s00787-020-01535-2.
- [37] Rose SA, Wass S, Jankowski JJ, Feldman JF, Djukic A. Impaired visual search in children with Rett syndrome. *Pediatr Neurol.* 2019; 92: 26-31. doi:10.1016/j.pediatrneurol.2018.10.002.
- [38] Cherenkova LV and Sokolova L V. Visual perception in preschool children with atypical development. *Neuropsychological Trends,* 2018. doi.org/10.7358/neur-2018-023-cher.
- [39] Brown AC, Crewther DP. Autistic children show a surprising relationship between global visual perception, non-verbal intelligence and visual parvocellular function, not seen in typically developing children. *Front Hum Neurosci.* 2017; 11: 239. doi:10.3389/fnhum.2017.00239.
- [40] Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. Motor coordination in autism spectrum disorders: a synthesis and meta-analysis. *J Autism Dev Disord.* 2010; 40: 1227-40. doi:10.1007/s10803-010-0981-3.
- [41] Semino S, Zanobini M, Usai MC. Visual memory profile in children with high functioning autism. *Appl Neuropsychol Child.* 2019; 10: 1-11. doi:10.1080/21622965.2019.1594231.
- [42] Funabiki Y, Shiwa T. Weakness of visual working memory in autism. *Autism Res.* 2018; 11: 1245-52. doi:10.1002/aur.1981.
- [43] Zhou R, Xie X, Wang J, Ma B and Hao X. Why do children with autism spectrum disorder have abnormal visual perception? *Front. Psychiatry.* 2023; 14: 1087122. doi:10.3389/fpsyg.2023.1087122.
- [44] Mayes SD, Calhoun SL. Learning, attention, writing, and processing speed in typical children and children with ADHD, autism, anxiety depression, and oppositional-defiant disorder. *Child Neuropsychol.* 2007; 13: 469-93.
- [45] Martin NA. Test of visual perceptual skills (3rd Ed). Novato, CA: American Therapy Publications. 2006.
- [46] Ruth VD Hallen, C Manning, Evers, K. *et al.* Global motion perception in autism spectrum disorder: A meta-analysis. *J Autism Dev Disord.* 2019; 49: 4901-18. doi.org/10.1007/s10803-019-04194-8.

Items in AXIS Tool	Vetravan J et al. ²⁹	Hallen RV et al. ²⁷	Brown A C & Crewther DP ³⁹	Cherenkova L V et al. ³⁸	DiCriscio A S and Troiani V ³⁰	Jobs E N et al. ³⁴	Gunal A et al. ²⁵	Guy J et al. ²⁸	Rose S A et al. ³⁷	Seernani D et al. ³⁶	Chi I J et al. ²⁶	Wuang Y P et al. ³¹	DiCriscio A S and Troiani V ³²	Liu C et al. ²⁴	Faber L et al. ³³	Lin LY et al. ³⁵
Does the response rate raise concerns about non-response bias?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
If appropriate, was information about non-responders described?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Were the results internally consistent?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the results for the analyses described in the methods, presented?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the authors' discussions and conclusions justified by the results?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the limitations of the study discussed?	+	-	-	-	+	+	+	-	+	+	+	+	+	+	+	+
Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Was ethical approval or consent of participants attained?	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+

 : YES,
  : 'NO',
  : DO NOT KNOW

Improvement in *Neisseria gonorrhoeae* culture using modified fastidious broth

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ABSTRACT

Background: Culture of *Neisseria gonorrhoeae* is essential for antimicrobial susceptibility testing and drug resistance surveillance. However, the success rate for *N. gonorrhoeae* culture from samples collected at sexually transmitted disease clinics is low. Moreover, culturing this fastidious organism can be challenging.

Objective: This study aimed to develop and evaluate a modified fastidious broth (mFB) for improved preservation and culture of *N. gonorrhoeae* that would serve as both a transport medium for specimen collection from patients with suspected gonococcal infections and a growth enhancer for *N. gonorrhoeae* culture.

Materials and methods: The mFB was evaluated using five standard bacteria strains at a concentration of 10^5 , 10^3 , and 10^1 CFU/ml: *N. gonorrhoeae*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Escherichia coli*, and *Staphylococcus saprophyticus*. After that, the mFB was used to collect specimens from 29 patients (77 samples) at the Venereal Disease Clinic at Mae Sot Hospital in Tak Province, Thailand, between October 2023 and February 2024. A total of 77 specimens were divided into 2 groups according to the gram-negative diplococci in Gram stain: 1) positive results (8 specimens) and 2) negative results (69 specimens). Furthermore, the *N. gonorrhoeae* culture was compared by using mFB on Chocolate agar (CA) and the direct plate specimen culture on Thayer Martin agar (TMA).

Results: The results showed that the mFB could inhibit the growth of *E. coli*, *L. monocytogenes*, *S. agalactiae*, and *S. saprophyticus* but did not affect the growth of *N. gonorrhoeae* and significantly enhanced its growth. Using mFB, *N. gonorrhoeae* recovered 100% (8/8) of the positive Gram stain results from 77 clinical specimens, while direct TMA culture only recovered 75% (6/8). In addition, mFB enabled the detection of *N. gonorrhoeae* in 2 of the 69 Gram stain-negative specimens that were negative by direct TMA culture.

Conclusion: *N. gonorrhoeae* culture using mFB, followed by subculture on CA, indicated that the mFB can preserve *N. gonorrhoeae* in clinical specimens during delivery to the laboratory and promote its growth. This has the potential to improve gonorrhea diagnosis and treatment with appropriate antibiotics, as well as enhance surveillance of antimicrobial-resistant gonorrhea.

Introduction

Gonorrhea is the second most common sexually transmitted infection caused by a gram-negative bacterium called *Neisseria gonorrhoeae*, which is primarily transmitted through vaginal, oral, and anal sex. It remains a significant public health concern globally after *Chlamydia trachomatis* infection in Thailand and worldwide.^{1,2} Most cases of gonorrhea are asymptomatic; an untreated infection can cause severe complications.³ Although it is treatable and can be cured with some antibiotics, drug

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resistance in *N. gonorrhoeae* has been identified and reported.^{4,5} There was evidence of antibiotic resistance in this organism due to increased treatment without carefully considering the specific antibiotics used.⁴ The emergence of antimicrobial resistance in *N. gonorrhoeae* is making treatment of gonorrhea more challenging, with the risk of being untreatable. While ceftriaxone is the last option for first-line empirical monotherapy of gonorrhea, the first gonococcal isolates with ceftriaxone resistance along with high-level azithromycin resistance were identified in England and Australia in 2018.⁶ Furthermore, the increasing minimal inhibitory concentration (MIC) of ceftriaxone, cefixime, and azithromycin for *N. gonorrhoeae* antimicrobial susceptibility was reported from Thailand in 2023.⁷ The rational use of antibiotics and the development of new ones are critical to reducing this imminent threat.

N. gonorrhoeae culture is essential for antimicrobial susceptibility testing in infection treatment. It provides essential information for appropriate gonorrhea treatment and is vital for monitoring antimicrobial resistance. Specimen collection for *N. gonorrhoeae* culture must be done by a clinician who uses a swab or loop to collect specimens from patients before being sent to the laboratory for gonorrhea diagnosis using Gram stain and culture with special media. Moreover, *N. gonorrhoeae* is a fastidious pathogen and does not tolerate dehydration, which does not grow well in standard liquid media.⁸ Thayer-Martin agar (TMA) is a unique culture medium for *N. gonorrhoeae*, providing the necessary nutrients to enhance *N. gonorrhoeae* growth. Therefore, the utilization of an enrichment broth medium is recommended to improve the sensitivity of cultures that may contain small numbers of these organisms.⁹

To address this problem, we developed a new liquid enrichment medium: modified fastidious broth (mFB), formulated to preserve and enhance the growth of *N. gonorrhoeae* from clinical specimens during transportation to the laboratory and to select and enhance

N. gonorrhoeae growth in culture.

Materials and methods

Bacterial strains

Five standard bacteria strains: *N. gonorrhoeae* ATCC 49226, *Escherichia coli* ATCC 25922, *Staphylococcus saprophyticus* ATCC 19701, *Listeria monocytogenes* ATCC 19115, and *Staphylococcus agalactiae* ATCC 12386 were included in this study. They were obtained from the Thailand Biodiversity Center and the National Center for Genetic Engineering and Biotechnology. Freshly collected cultures were obtained from the original frozen stock cultures on chocolate agar (CA) for 24 hours to ensure the purity of colonies. They used VITEK® 2 COMPACT (Biomerieux, France) for identification before testing.

Clinical strains

The clinical specimens were collected from 29 patients (5 males and 24 females) with urogenital symptoms, primarily urethral or vaginal discharge, who visited the Venereal Disease Clinic at Mae Sot Hospital in Tak Province, north-west Thailand, between October 2023 and February 2024. The Naresuan University Institutional Review Board ethically approved this study, and informed consent was obtained from all patients before specimen collection. Seven patients (5 males and 2 females) were diagnosed with gonorrhea after finding gram-negative diplococci by Gram stain. They were treated with 500 mg of ceftriaxone by injection. Twenty-two patients (females) were diagnosed with non-gonorrhea infections and received treatment based on their symptoms.

A total of 77 specimens were collected from 29 patients, composed of the urethra (29), cervical (24), and vagina (24), as shown in Table 1. All specimens were screened for gonorrhea infection before culture using a Gram stain. Then, they were inoculated on Thayer-Martin agar and in modified fastidious broth for *N. gonorrhoeae* culture.

Table 1. Type of specimens and Gram stain results of 77 specimens.

Sex (N)	Gram-negative diplococci						Total
	Positive (N=8)			Negative (N=69)			
	Urethra	Cervix	Vagina	Urethra	Cervix	Vagina	
Male (5)	5	0	0	0	0	0	5
Female (24)	1	2	0	23	22	24	72
Total (29)	6	2	0	23	22	24	77

Modified fastidious broth

The fastidious broth to enhance and amplify fastidious bacteria, especially *Neisseria* spp., was developed using Brain Heart Infusion broth as a liquid medium base, supplemented with hematin with an X factor (hemin). This solution was autoclaved at 121 °C for 15 min. Then, the Isovitalex Enrichment, containing vitamins, amino acids, co-enzymes, dextrose, ferric ions, and other elements, was added. Moreover, the Vancomycin-Colistin-Nystatin (V-C-N) inhibitor was used to suppress normal flora

including fungi. After fastidious broth preparation, 5 ml aliquots were dispensed into 10 ml sterile culture tubes and stored at 4 °C.

Evaluation of modified fastidious broth in selection and growth enhancement

Five bacterial suspensions (*N. gonorrhoeae* ATCC 49226, *E. coli* ATCC 25922, *S. saprophyticus* ATCC 19701, *L. monocytogenes* ATCC 19115, and *S. agalactiae* ATCC 12386) were adjusted to the 0.5 McFarland standard

using sterile saline (0.45% NaCl). Ten-fold serial dilutions of 10^5 , 10^3 , and 10^1 CFU/mL were prepared in triplicate. The bacterial growth-enhancing ability of mFB was determined by visual turbidity after 2-, 24-, and 48-hr incubation at 35 °C with 5% CO₂, compared to mFB that did not contain organisms. Moreover, the typical colonies of each organism after subculture on CA were observed and identified using Gram stain and VITEK® 2 COMPACT (Biomérieux, France) after incubation at 35 °C with 5% CO₂ for 24 and 48 hrs.

Comparison of *N. gonorrhoeae* culture from clinical specimens between direct culture and modified culture using mFB

Direct culture on Thayer Martin agar

A total of 77 specimens were directly plated on TMA within 1 hour after collection and incubated at 35 °C with 5% CO₂ according to the Manual of Clinical Microbiology, 7th Edition.¹⁰ The typical colonies of *N. gonorrhoeae* on TMA were observed at 24 and 48 hrs, identified using Gram stain and oxidase testing, and confirmed using NH VITEK® 2 COMPACT (Biomérieux, France).

Modified culture using mFB

In the same way, 77 specimens were collected and immediately put into mFB. Then they were incubated at 35 °C with 5% CO₂ within 1 hr after collection. The signs of growth were monitored by observing turbidity and

subculturing on CA after 2-, 24-, and 48-hr incubation at 35 °C with 5% CO₂. The typical colonies of *N. gonorrhoeae* on CA were observed at 24 and 48 hrs and were identified in the same manner as the previously identified colonies on TMA.

Results

Preservation, selection, and enhancing growth of mFB

The ability of mFB to enhance the growth is shown in Table 2. It indicates that mFB effectively selected, supported, and enhanced the growth of *N. gonorrhoeae*. All inoculums of *N. gonorrhoeae* were visually detectable by turbidity within 24 hrs of incubation. In contrast, none of the inoculums of the four standard bacterial strains (*E. coli*, *S. saprophyticus*, *L. monocytogenes*, and *S. agalactiae*) were detectable. This mFB also enhanced the growth of *N. gonorrhoeae* better than four bacterial strains after subculture on CA. mFB completely inhibited the growth of gram-negative bacteria such as *E. coli*, which could not grow in the mFB. In addition, the mFB could support and enhance *N. gonorrhoeae* growth in the early incubation (2 hrs), with the colonies present on CA at approximately 10^3 and 10^5 CFU/ml. In contrast, there was a bit of enhanced growth in the early incubation (2 hrs) of *L. monocytogenes* and *S. agalactiae* at approximately 10^5 CFU/mL concentration, and their growth rates began to decline after 24 hrs of incubation.

Table 2. Growth enhancing of modified fastidious broth.

Organisms	Inoculum (CFU/ml)	Turbidity			Growth results on CA		
		2 hrs	24 hrs	48 hrs	2 hrs	24 hrs	48 hrs
<i>E. coli</i>	10^5	×	×	×	-	-	-
	10^3	×	×	×	-	-	-
	10^1	×	×	×	-	-	-
<i>S. saprophyticus</i>	10^5	×	×	×	+ (1) ³	-	-
	10^3	×	×	×	-	-	-
	10^1	×	×	×	-	-	-
<i>L. monocytogenes</i>	10^5	×	×	×	+ (1) ⁴	+ (1) ²	+ (1) ¹
	10^3	×	×	×	+ (1) ²	+ (1) ¹	-
	10^1	×	×	×	-	-	-
<i>S. agalactiae</i>	10^5	×	×	×	+ (1) ⁴	+ (1) ²	-
	10^3	×	×	×	+ (1) ¹	-	-
	10^1	×	×	×	-	-	-
<i>N. gonorrhoeae</i>	10^5	×	✓	✓	+ (1) ³	+ (1) ⁴	+ (1) ⁴
	10^3	×	✓	✓	+ (1) ²	+ (1) ⁴	+ (1) ⁴
	10^1	×	✓	✓	-	+ (1) ⁴	+ (1) ⁴

Note: (✓): visually (turbidity) detecting, (×): no visually (turbidity) detecting, (+): organism growth on CA after subculture from incubated mFB, (-): organism no growth on CA after subculture from incubated mFB, (A)^b, A: numbers in parentheses represent the earliest times (in days) at which growth, b: organism grading on CA (1; rare (<10 colonies), 2: few (organism growth 1/4 plate, >10 colonies), 3: moderate (organism growth 2/4 plate), 4: many [organism growth 3/4 plate]).

Comparison of *N. gonorrhoeae* culture from clinical specimens between TMA and mFB

The *N. gonorrhoeae* colonies on CA were observed after subculture from mFB at a 2-hr incubation period in all 8 specimens (100%; 6 specimens from the urinary tract and 2 specimens from the cervix), as shown in Table 3. In contrast, when using directed culture on TMA, the *N. gonorrhoeae* colonies were found in 6 out of 8 specimens (75%; 4 specimens from the urinary tract and 2 specimens from the cervix), while 2 out of 8 specimens from the male urethra (25%) showed no signs of *N. gonorrhoeae* growth.

For 69 samples that did not find gram-negative diplococci (gram stain negative results), there were no growth of *N. gonorrhoeae* when using directly cultured TMA. However, *N. gonorrhoeae* growth was observed on CA after subculture from two of the mFB incubated

specimens from the vaginal specimens (2.90%). When comparing the culture results using the Z test, there was a non-significant difference between the two methods (Z-score of 1.0564 and a $p=0.289$) (data not shown).

All 6 *N. gonorrhoeae* isolates growth on TMA and 10 *N. gonorrhoeae* isolates growth on CA (after subculture using mFB) were confirmed by Gram stain and identification using oxidase test, catalase test, and VITEK 2 NH Identify CARD (VITEK® 2 COMPACT, Biomerieux). Moreover, all ten isolates were tested for antimicrobial susceptibility by disk diffusion with ciprofloxacin (5 µg), tetracycline (30 µg), ceftriaxone (30 µg), and penicillin (10 units).¹¹ They showed that all isolates were resistant to ciprofloxacin, tetracycline, and penicillin but still susceptible to ceftriaxone (data not shown).

Table 3. Comparison of *N. gonorrhoeae* culture between using TMA and mFB.

Type of culture media	Gram's stain positive (N=8)		Gram's stain negative (N=69)		Total
	Culture Positive	Culture Negative	Culture Positive	Culture Negative	
Modified Fastidious broth (followed by subculture on CA)					
Urethra	6	0	0	23	29
Cervix	2	0	0	22	24
Vagina	0	0	2	22	24
Total	8 (100%)	0	2 (2.90%)	67 (97.10%)	77
Thayer Martin agar					
Urethra	4	2	0	23	29
Cervix	2	0	0	22	24
Vagina	0	0	0	24	24
Total	6 (75%)	2 (25%)	0	69 (100%)	77

Note: Gram stain positive: found gram-negative diplococci, Gram stain negative: not found gram-negative diplococci, Culture Positive: *N. gonorrhoeae* growth on culture media, Culture negative: no *N. gonorrhoeae* colonies on culture media.

Discussion

The enhancing ability of mFB was examined for visual signs of growth both in the mFB tube and after subculture on CA. We found that the mFB preserved and enhanced recovery of a small number of *N. gonorrhoeae* is significantly intriguing (Tables 2 and 3). The results demonstrated that mFB, with a low inoculum of 10^1 CFU/ml, improved the recovery of *N. gonorrhoeae*, allowing them to grow in large numbers on CA after subculturing from incubated mFB. On the other hand, a report by Cartwright CP et al. found that FB enhanced recovery of 10^2 CFU/ml by showing visual signs of growth in FB after a 96-hour incubation period.¹² Moreover, the data demonstrated that VCN inhibitors in the mFB can affect the growth of other organisms, including *E. coli*, *S. saprophyticus*, *L. monocytogenes*, and *S. agalactiae*, which are usually found in vagina and urinary tract systems.¹³⁻¹⁵ However, these inhibitors did not affect *N. gonorrhoeae* growth.¹⁶ This may be due to *N. gonorrhoeae* having intrinsic resistance mechanisms to vancomycin, trimethoprim, and colistin.¹⁷ This implied the possibility of using mFB as a transport and selective medium for *N. gonorrhoeae*.

For *N. gonorrhoeae* culture from clinical specimens, the efficiency of mFB in growth enhancement was more significant than using a direct plate specimen on TMA (Table 3). However, statistical analysis indicated no significant difference between the two media. One limitation of this study is the small sample size. Future studies should aim to collect more samples, particularly from patients with *N. gonorrhoeae* infections.

In addition, the colonies of *N. gonorrhoeae* were detected on CA after subculturing from the mFB of two specimens with negative gram stain results initially. Possible causes could be an insufficient specimen, a small organism, or smear preparation.¹⁸ These suggest that its ability was both to preserve and enhance the growth of this organism. The incubation in mFB before subculture on CA could improve the likelihood of *N. gonorrhoeae* detection in the specimen compared to direct culture on TMA. This research demonstrated that the mFB enhanced the growth of small organism specimens and enabled their cultivation on readily available CA medium, potentially eliminating the need for TMA in culture procedures. Furthermore, a microbiology laboratory can prepare this mFB in-house

from the essential media or supplement available, which can help reduce the cost of *N. gonorrhoeae* culture.

This study has attempted to develop a liquid culture medium known as modified fastidious broth (mFB). The findings suggest that mFB can preserve the *N. gonorrhoeae* in specimens during transport to the laboratory. Additionally, this mFB could enhance the likelihood of detecting *N. gonorrhoeae* in culture from the patient's specimen. The inhibitors in mFB are likely to inhibit the growth of any bacteria that may be contaminants. However, it did not affect the growth of *N. gonorrhoeae*. As a result, we can test for drug susceptibility, which will provide future guidelines for treatment and surveillance of antibiotic resistance.

Conclusion

In summary, culturing *N. gonorrhea* using mFB followed by subculture on CA may improve gonorrhea diagnosis. It also provides the low cost of medium preparation, simplicity in specimen collection, and the ability to conduct drug susceptibility testing. As a result, it not only facilitates appropriate gonorrhea treatment but also supports surveillance of antimicrobial resistance in *N. gonorrhea*.

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References

- [1] Lin EY, Adamson PC, Klausner JD. Epidemiology, Treatments, and Vaccine Development for Antimicrobial-Resistant *Neisseria gonorrhoeae*: Current Strategies and Future Directions. *Drugs*. 2021; 81(10): 1153-69.
- [2] World Health Organization. Report on global sexually transmitted infection surveillance 2018.
- [3] Keshvani N, Gupta A, Incze MA. I am worried about gonorrhea: what do i need to know? *JAMA Intern Med*. 2019; 179(1): 132. doi.org/10.1001/jamainternmed.2018.4345.
- [4] Fingerhuth SM, Bonhoeffer S, Low N, Althaus CL. Antibiotic-Resistant *Neisseria gonorrhoeae* Spread Faster with More Treatment, Not More Sexual Partners. *PLoS Pathog*. 2016; 12: 1-15. doi.org/10.1371/journal.ppat.1005611, PMID: 27196299
- [5] Unemo M, Lahra MM, Cole M, Galarza P, Ndowa F, Martin I, et al. World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. *Sex Health*. 2019; 16(5): 412-25.
- [6] Unemo M, Golparian D, Eyre DW. Antimicrobial Resistance in *Neisseria gonorrhoeae* and Treatment of Gonorrhea. *Methods Mol Biol*. 2019; 1997: 37-58. doi: 10.1007/978-1-4939-9496-0_3. PMID: 31119616.
- [7] Pleininger S, Indra A, Golparian D, Heger F, Schindler S, Jacobsson S, et al. Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* causing possible gonorrhoea treatment failure with ceftriaxone plus azithromycin in Austria, April 2022. *Euro Surveill*. 2022; 27(24): 2200455. doi: 10.2807/1560-7917.ES.2022.27.24.220045
- [8] Kittiyaowamarn R, Girdthep N, Cherdtrakulkiat T, Sangprasert P, Tongtoyai J, Weston E, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility trends in Bangkok, Thailand, 2015-21: Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP). *JAC Antimicrob Resist*. 2023; (6): dlad139. doi: 10.1093/jacmr/dlad139.
- [9] Ison CA, Golparian D, Saunders P, Chisholm S, Unemo M. Evolution of *Neisseria gonorrhoeae* is a continuing challenge for molecular detection of gonorrhoea: False negative gonococcal porA mutants are spreading internationally. *Sex Transm Infect*. 2013; 89: 197-201. doi.org/10.1136/sextrans-2012-050829 PMID: 23241969
- [10] Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH editors. *Manual of Clinical Microbiology* 7th Ed. Washington, DC: ASM Press; 1999. p.64-104: 777-806.
- [11] Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*, 32nd Ed. CLSI supplement M100 (ISBN 978-1-68440-134-5 [Print]; ISBN 978-1-68440-135-2 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2022.
- [12] Cartwright CP, Stock F, Gill VJ. Improved enrichment broth for cultivation of fastidious organisms. *J Clin Microbiol*. 1994; 32(7): 1825-6. doi: 10.1128/jcm.32.7.1825-1826.1994.
- [13] Kazemi Rad S, Assmar M, Mirpour M, Razavi MR. Evaluation of Chitosan Nanoparticle Antimicrobial Effect on Isolated *Listeria monocytogenes* Bacteria from Pregnant Women and *L. monocytogenes* ATCC 7644 Iran J Public Health 2022; 51(12): 2783-90. doi: 1018502/ijphv51i1211469 PMID: 36742246; PMCID: PMC9874196.
- [14] Khademi F, Sahebkar A. Group B streptococcus drug resistance in pregnant women in Iran: a meta-analysis Taiwan J Obstet Gynecol 2020; 59(5): 635-42 doi: 101016/jtjog202007002 PMID: 32917310.
- [15] Zhou Y, Zhou Z, Zheng L, Gong Z, Li Y, Jin Y, et al. Urinary Tract Infections Caused by Uropathogenic *Escherichia coli*: Mechanisms of Infection and Treatment Options. *Int J Mol Sci*. 2023; 24(13): 10537. doi: 10.3390/ijms241310537.
- [16] Thayer JD, Martin JE Jr. Improved medium selective for cultivation of *N. gonorrhoeae* and *N. meningitidis*. *Public Health Rep* (1896). 1966; 81(6): 559-62. PMID: 4957043; PMCID: PMC1919807.
- [17] Unemo M, Shafer WM. Antimicrobial Resistance in *Neisseria gonorrhoeae* in the 21st Century: Past, Evolution, and Future. *Clin Microbio Rev*. 2014; 27(3):587-613. doi: 10.1128/CMR.00010-14
- [18] Samuel LP, Balada-Llasat JM, Harrington A, Cavagnolo R. Multicenter Assessment of Gram Stain Error Rates. *J Clin Microbiol*. 2016; 54(6): 1442-7. doi: 10.1128/JCM.03066-15 PMID: 26888900; PMCID: PMC4879281.

Evaluation of a commercial multiplex real-time PCR panel for identification environmental water antibiotic-resistant bacteria in hemoculture bottles

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ABSTRACT

Background: Antimicrobial resistance (AMR) is a major public health problem worldwide, and it is increasing, especially in developed and developing countries, including Thailand. Sepsis is a crisis and emergency causing the death of patients with a high mortality rate of 1 in 5 of the global population. Using inappropriate antimicrobial drugs to treat infections increases the chance of drug resistance in the microorganisms, and precise and rapid treatment is essential for patient management.

Objective: This cooperative study aims to evaluate a commercial multiplex real-time PCR panel, QIAstat-Dx BCID GN Plus AMR Panel, to detect antimicrobial-resistant genes in the bloodstream.

Materials and methods: Thirty bacterial samples were used to simulate bloodstream infections. The comparison between the QIAstat-Dx BCID GN Plus AMR Panel and the conventional PCR method was revealed.

Results: Both methods gave concordant results for 12 samples, while results for 15 were discordant. Three samples could not be detected using the QIAstat-Dx BCID GN Plus AMR Panel because *ebc* gene is not included. The QIAstat-Dx BCID GN Plus AMR Panel revealed a sensitivity, specificity, positive predictive value, and negative predictive value of 91.50%, 93.30%, 74.10%, and 98.50%, respectively.

Conclusion: The study indicated that the QIAstat-Dx BCID GN Plus AMR Panel Cartridge can detect common antimicrobial-resistant genes from the bloodstream. However, additional resistant genes should be included in the panel to cover various highly prevalent antimicrobial-resistant genes based on geographical location.

Introduction

Antimicrobial-resistant bacteria have emerged as a significant global public health concern, with a continuously increasing trend observed in developed and developing countries, including Thailand. The majority of pathogens responsible for infectious diseases in Thai communities,¹ as reported by the Ministry of Public Health, Department of Health, Office of Environmental Health in 2017, were implicated in bloodstream infections. The problem of antimicrobial resistance is multifactorial, with factors such as the excessive use of antibiotics and the discharge of contaminated water or waste materials from

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hospitals or factories into the environment contributing to the escalation.¹

In 2019, the global Antimicrobial Resistance (AMR) Situation Report revealed that 4.95 million people died from AMR infection, with one in every five children under 5 years old. In 2019, Thailand reported 10,800 deaths attributed to AMR and an additional 43,900 deaths related to AMR.² Sepsis is a critical emergency leading to a high mortality rate, affecting 1 in 5 individuals globally. In Thailand, sepsis stands as the primary cause of death among hospitalized patients, with a tendency to increase.³ Gram-negative bacteria pose a significant medical challenge due to their resistance to antimicrobial agents, especially *Escherichia coli*, *Klebsiella pneumoniae*, other Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.⁴ Over the past decade, these organisms have developed increased drug resistance, leading to prolonged treatment durations to eliminate them.⁵

Among these Gram-negative bacteria, AmpC beta-lactamase (*ampC*) expression in bacteria is a resistance mechanism producing beta-lactamase, an enzyme with similar activity as extended-spectrum beta-lactamases (ESBLs).⁶ Beta-lactamases can hydrolyze the beta-lactam ring, thereby inactivating the antibiotic and conferring resistance to most beta-lactam antibiotics, including penicillin, narrow-spectrum and extended-spectrum cephalosporin and monobactams.⁷ However, AmpC confers resistance to cephamycin and is not inhibited by beta-lactamase inhibitors. Therefore, beta-lactamase can cause bacteria to become resistant to many drugs.

The main causes of hospital-acquired infections are *K. pneumoniae* and *E. coli*, with limited drugs available for treatment. In beta-lactamase-producing *E. coli* strains, AMR can be verified by phenotypic expression characteristics and by detecting the beta-lactamase genes. Furthermore, Amp C origin - *Enterobacter cloacae* (EBC) is included in the beta-lactamase class C group.⁸ Primary genes responsible for beta-lactam resistance include ambler classification class A enzymes, such as cefotaximase (CTX-M), sulfhydryl variable (SHV), temoniera beta-lactamase (TEM), *Pseudomonas* extended resistance beta-lactamase (PER), Vietnamese extended-spectrum beta-lactamase (VEB) and Guiana extended-spectrum beta-lactamase (GES). Recently, beta-lactamases have emerged that are active against carbapenems (carbapenemases), which are found primarily in enterobacterales. The three types of carbapenemases comprise *K. pneumoniae* carbapenemases (KPCs), metallo-beta-lactamases (MBLs), and oxacillinases (OXAs). The KPCs belong to the serine class A (functional group 2f) beta-lactamases and are resistant to all beta-lactam drugs but may still be affected by beta-lactamase inhibitors. MBLs are class B beta-lactamases, functional group 3a, capable of hydrolyzing all beta-lactam drugs but are not inactivated by beta-lactamase inhibitors. The most widely distributed MBLs are the IMP-1 (for imipenem resistance) and VIM-1 (Verona integron encoded MBL) types. MBL has recently been identified, mainly in *E. coli* strains, and has

been designated NDM-1 (New Delhi MBL). The infections caused by carbapenem-resistant enterobacterales (CRE) strains have been associated with up to 71% in-hospital mortality.^{9,10}

The widespread dissemination of colistin resistance has recently garnered significant attention from the scientific community due to its critical role as the last line of defense against carbapenem-resistant enterobacterales infections and its potential for horizontal gene transfer. The mobilized colistin resistance (*mcr*) gene has been identified as the key gene responsible for this unique form of resistance. Colistin, also known as polymyxin E, is an antimicrobial agent effective against various gram-negative bacilli, particularly those in the enterobacteriaceae famil.¹¹

Aminoglycoside-modifying enzymes (AMEs) are another kind that confer antibiotic resistance through enzymatic modifications, changing the structure of aminoglycoside antibiotics and reducing their binding affinity to the 30S ribosomal subunit. Aminoglycosides bind to the aminoacyl-tRNA recognition site (A-site) of the 30S ribosomal subunit, inhibiting polypeptide synthesis and subsequent bacterial cell death. AMEs are commonly expressed by the aminoglycoside resistance methylase (*armA*) and aminoglycoside 3-N-acetyltransferase (*aac*) genes.¹²

Antimicrobial drug use to treat infectious diseases usually increases the chance of drug resistance as a survival mechanism for the pathogen.¹³ Therefore, Accurate diagnosis and early testing for AMR are crucial for selecting the proper treatment quickly, helping to reduce the severity of the disease and lower the risk of death. Therefore, this research focused on evaluating the effectiveness of the multiplex real-time PCR panel in detecting drug-resistant genes in bloodstream infections.

Materials and methods

Bacterial identification, antimicrobial susceptibility testing, and preparation

A total of 30 bacterial strains were used in this research, including 28 strains from Walter Reed Army Institute of Research—Armed Forces Research Institute of Medical Sciences (WRAIR-AFRIMS) and 2 standard strains (*E. coli* ATCC 8739 and *E. coli* ATCC 25922), which were used as negative controls. All 28 bacterial strains were isolated from environmental water.

Each bacterial isolate was initially identified for its species and antimicrobial susceptibility testing (AST) using the BD Phoenix™M50 automated microbiology system (BD Diagnostic Systems, Sparks, MD). Antimicrobial susceptibility results were interpreted according to the CLSI, EUCAST, and La Société française de microbiologie (SFM) guidelines.¹⁴⁻¹⁶ Conventional molecular detection of AMR genes was performed as described previously.¹⁷

Isolate preparation for the QIAstat-Dx BCID GN plus AMR panel

Each strain was cultured in tryptic soy broth (TSB) (Becton Dickinson, Sparks, MD, USA) at 37 °C for 24 hrs, then adjusted to a bacterial concentration of 1.0

McFarland (equivalent to $\sim 3.0 \times 10^8$ CFU/mL), and 1 mL was inoculated in a blood culture bottle (Becton Dickinson, Sparks, MD, USA) with 9 ml of human whole blood donor. The blood culture bottle was incubated in an automated blood culture system following the instruction of BD BACTEC™ (Becton Dickinson, Sparks, MD, USA) until the blood culture bottle showed positive.

At bottle positivity, 100 μ L of blood was withdrawn, placed in a microcentrifuge tube, and then transferred to the QIAstat-Dx BCID GN Plus AMR Panel cartridge (Qiagen, Thailand) included primers for detecting 18 resistance gene; AmpC, CTX-M, IMP, KPC, NDM, OXA-23, OXA-48 like, OXA-24/40, OXA-58, SHV, TEM, VIM, PER, *armA*, *acc (6')-Ib*, VEB, GES and SPM. Next, the QIAstat-Dx BCID GN Plus AMR Panel cartridge was inserted in the QIAstat-Dx Analyzer 1.0 (Qiagen, Thailand) based on real-time automated PCR assay.

Data analysis

The results of the QIAstat-Dx BCID GN Plus AMR Panel were compared to reference results generated by conventional PCR and antimicrobial drug susceptibility testing performed by WRAIR-AFIRMS. Statistical analyses were performed using STATA/BE, 18.0 Software, including sensitivity, specificity, and positive and negative predictive values. The limit of detection was defined as the lowest

concentration at which each target was detected $\geq 95\%$ of the time. At least 20 replicates were performed at the determined limit of detection concentration.

Results

Diagnostic performance of QIAstat-Dx BCID GN Plus AMR Panel in comparison with PCR

Eleven genes were detected using the QIAstat-Dx BCID GN Plus AMR Panel: CTX-M, GES, SHV, VEB, TEM, AmpC, NDM, OXA-23, OXA-48 like *armA* and *acc (6')-Ib*. This panel could not detect EBC, *mcr-3*, and OXA-resistant genes, as they are not part of the panel. When comparing the results of this panel to results from conventional PCR, 10 bacterial strains showed concordant results, 15 strains gave discordant results, and 3 strains carried resistant genes that the panel excluded (Table 1). The calculated values for sensitivity (91.50%), specificity (93.30%), positive predictive value (74.10%), negative predictive value (98.50%), and detection limit (3.0×10^8 CFU/mL) of the panel are shown in Table 2. The strength of agreement between QIAstat-Dx BCID GN Plus AMR Panel and PCR method for detecting drug-resistant genes was categorized as a substantial correlation with a kappa value of 0.71 (Table 2). The calculated values for each AMR gene are shown in Table 3.

Table 1. Comparison of bacterial drug resistance gene test results between conventional PCR and QIAstat-Dx BCID GN plus AMR panel.

No.	Pathogens	Beta-lactamases class A group (ESBL)												Beta-lactamases (class C group)				Carbapenem (class B group)				Carbapenem/Oxacillinase (class D group)						Aminoglycoside-modifying resistance gene				Mobilized colistin resistance gene	
		CTX-M		GES		SHV		VEB		TEM		AmpC		EBC		NDM		OXA		OXA-23		OXA-48 like		armA		aac (6')-Ib		mcr-3					
		PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.				
1	<i>Enterobacter cloacae</i> WOH-005-5	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	ND	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Neg	Neg	ND				
2	<i>Enterobacter cloacae</i> WOH-006-3	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	ND	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
3	<i>Escherichia coli</i> WOH-008-2	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
4	<i>Escherichia coli</i> WOH-009-6	Pos	Pos	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
5	<i>Escherichia coli</i> WOH-010-1	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
6	<i>Klebsiella pneumoniae</i> WOH-010-3	Pos	Pos	Neg	Neg	Neg	Neg	Pos	Neg	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Pos	ND	Neg	Neg	Neg	ND	Neg	ND	Pos	Neg	ND	ND				
7	<i>Acinetobacter baumannii</i> WOH-010-4	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Pos	Neg	ND	Neg	Neg	ND	Pos	ND	Neg	Neg	Neg	ND	ND				
8	<i>Klebsiella pneumoniae</i> WOH-010-5	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	Neg	ND	Neg	Pos	Neg	ND	ND				
9	<i>Enterobacter cloacae</i> WOH-010-6	Neg	Pos	Pos	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	ND	Neg	Neg	Pos	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
10	<i>Escherichia coli</i> WOH-010-9	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
11	<i>Klebsiella pneumoniae</i> WOH-010-10	Pos	Pos	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Pos	Neg	ND	Neg	Pos	ND	Neg	ND	Neg	Neg	Neg	ND	ND				
12	<i>Enterobacter cloacae</i> WOH-010-11	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Pos	Neg	ND	ND				
13	<i>Escherichia coli</i> WOH-010-12	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	ND	Neg	Neg	Pos	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
14	<i>Escherichia coli</i> WOH-010-13	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Pos	Neg	ND	ND				
15	<i>Klebsiella pneumoniae</i> WOH-010-14	Pos	Pos	Neg	Neg	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Pos	ND	Neg	Neg	Neg	ND	Neg	ND	Pos	Neg	ND	ND				
16	<i>Escherichia coli</i> WOH-010-15	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
17	<i>Escherichia coli</i> WOH-010-16	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Pos	Neg	ND	ND				
18	<i>Acinetobacter baumannii</i> WOH-010-17	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				
19	<i>Enterobacter cloacae</i> WOH-010-19	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg	ND	Neg	ND	Neg	Neg	ND	ND				

Pos = Positive / Neg = Negative / ND = Not determined

Table 1. Comparison of bacterial drug resistance gene test results between conventional PCR and QIAstat-Dx BCID GN plus AMR panel (continued).

No.	Pathogens	Beta-lactamases class A group (ESBL)										Beta-lactamases (class C group)			Carbapenem (class B group)			Carbapenem/Oxacillinase (class D group)						Aminoglycoside-modifying resistance gene				Mobilized colistin resistance gene	
		CTX-M		GES		SHV		VEB		TEM		AmpC		EBC		NDM		OXA		OXA-23		OXA-48 like		armA		aac (6')-Ib		mcr-3	
		PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.	PCR	Q.st.
20	<i>Enterobacter cloacae</i> WOH-010-20	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
21	<i>Enterobacter cloacae</i> WOH-010-21	Neg	Neg	Neg	Neg	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	ND	Pos	Pos	Neg	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
22	<i>Escherichia coli</i> WOH-010-23	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	ND	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
23	<i>Enterobacter cloacae</i> WOH-010-24	Neg	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Pos	Pos	Neg	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
24	<i>Escherichia coli</i> WOH-010-26	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
25	<i>Klebsiella pneumoniae</i> WOH-010-27	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
26	<i>Enterobacter cloacae</i> WOH-010-31	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
27	<i>Enterobacter cloacae</i> WOH-010-32	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Pos	Pos	Neg	ND	Neg	Pos	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
28	<i>Escherichia coli</i> WOH-010-33	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
29	<i>Escherichia coli</i> ATCC 8739	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND
30	<i>Escherichia coli</i> ATCC 25922	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	ND	ND	Neg	Neg	Neg	Neg	ND	ND	Neg	Neg	ND	ND

Pos = Positive / Neg = Negative / ND = Not determined

Table 2. QIAstat-Dx BCID GN Plus AMR Panel performance to detect AMR genes in comparison with conventional PCR

Performance	QIAstat-Dx BCID GN Plus AMR Panel
Sensitivity	91.50 % (79.60 % – 97.60 %)*
Specificity	93.30% (89.10 % – 96.20 %)*
Positive predictive value (PPV)	74.10 % (61.00 % – 84.70 %)*
Negative predictive value (NPV)	98.50 % (96.20 % – 99.60 %)*
Detection limit	3.0 x 10 ⁸ CFU/ml
Agreement between tests kappa	0.71 (0.66 - 0.76)*

*Data are presented as percentage (95% confidence interval; CI) for all parameters except the detection limit (CFU/ml).

Table 3. QIAstat-Dx BCID GN Plus AMR Panel performance to detect each AMR genes in comparison with conventional PCR.

Drug-resistant genes	Performance of QIAstat-Dx BCID GN Plus AMR Panel			
	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
CTX-M	100.00% (73.50% - 100.00%)*	94.40% (72.70% - 99.90%)*	92.30% (64.00% - 99.80%)*	100.00% (80.50% - 100.00%)*
GES	83.30% (35.90% - 99.60%)*	100.00% (85.80% - 100.00%)*	100.00% (47.80% - 100.00%)*	96.00% (79.60% - 99.90%)*
SHV	100.00% (47.80% - 100.00%)*	88.00% (68.80% - 97.50%)*	62.50% (24.50% - 91.50%)*	100.00% (84.60% - 100.00%)*
VEB	66.70% (9.40% - 99.20%)*	85.20% (66.30% - 95.80%)*	33.30% (4.30% - 77.70%)*	95.80% (78.90% - 99.90%)*
TEM	92.30% (64.00% - 99.80%)*	100.00% (80.50% - 100.00%)*	100.00% (73.50% - 100.00%)*	94.40% (72.70% - 99.90%)*
AmpC	50.00% (1.30% - 98.70%)*	100.00% (87.70% - 100.00%)*	100.00% (2.50% - 100.00%)*	96.60% (82.20% - 99.90%)*
NDM	100.00% (47.80% - 100.00%)*	84.00% (63.90% - 95.50%)*	55.60% (21.20% - 86.30%)*	100.00% (83.90% - 100.00%)*
OXA-48 like	100.00% (2.50% - 100.00%)*	96.60% (82.20% - 99.90%)*	50.00% (1.30% - 98.70%)*	100.00% (87.70% - 100.00%)*

*Data are presented as percentage (95% confidence interval; CI)

Sensitivity, specificity, PPV, and NPV were not calculated for OXA, OXA-23, EBC, *armA*, *aac(6')*-I, and MCR-3 due to insufficient data.

Discrepancies between QIAstat-Dx BCID GN Plus AMR Panel and antimicrobial susceptibility testing

Thirteen antibiotic drugs were designated for antimicrobial susceptibility testing, and the results are presented in Table 4. The correlation between the antimicrobial susceptibility testing and the panel is presented in Table 5, 6 and 7. All drug-resistant genes of the beta-lactamase group showed positive results with 100.00% concordance with phenotypic resistance to ampicillin. Some of these genes also showed concordance with cefazolin, ampicillin-sulbactam, cefepime, ceftazidime,

ceftazidime-avibactam, and piperacillin-tazobactam resistance. For the carbapenem/oxacillinase group, the NDM and OXA-23 genes showed positive results with 100.00% concordance with resistance to ertapenem, imipenem, and meropenem. In contrast, the OXA-48-like gene showed a positive result with 100.00% concordance with resistance to ertapenem and imipenem. The *armA* gene of the aminoglycoside group showed positive results with 100.00% concordance with resistance to amikacin and gentamicin.

Table 4. Antimicrobial drug susceptibility testing results

No.	Pathogens	Beta-lactamases drugs							Carbapenem drugs			Aminoglycoside drugs		Colistin drug
		Ampicillin	Ampicillin-Sulbactam	Cefazolin	Cefepime	Ceftazidime	Ceftazidime-Avibactam	Piperacillin-Tazobactam	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Colistin
1	<i>Enterobacter cloacae</i> WOH-005-5	R	R	R	S	S	S	S	S	I	S	S	S	R
2	<i>Enterobacter cloacae</i> WOH-006-3	R	R	R	S	S	S	S	S	I	S	S	S	X
3	<i>Escherichia coli</i> WOH-008-2	R	I	X	S	S	S	S	S	S	S	S	S	X
4	<i>Escherichia coli</i> WOH-009-6	R	S	R	R	I	S	S	S	S	S	S	S	X
5	<i>Escherichia coli</i> WOH-010-1	R	I	X	S	S	S	S	S	S	S	S	R	X
6	<i>Klebsiella pneumoniae</i> WOH-010-3	R	R	R	R	R	S	R	R	R	I	S	R	X
7	<i>Acinetobacter baumannii</i> WOH-010-4	R	R	R	R	R	R	R	R	R	R	R	R	X
8	<i>Klebsiella pneumoniae</i> WOH-010-5	R	R	R	S	R	S	S	R	I	R	S	R	X
9	<i>Enterobacter cloacae</i> WOH-010-6	R	R	R	R	R	R	R	R	R	R	R	R	X
10	<i>Escherichia coli</i> WOH-010-9	R	I	R	S	S	S	S	S	S	S	S	R	X
11	<i>Klebsiella pneumoniae</i> WOH-010-10	R	R	R	R	R	R	R	R	R	R	R	R	X
12	<i>Enterobacter cloacae</i> WOH-010-11	R	R	R	S	S	S	S	R	S	S	S	I	R
13	<i>Escherichia coli</i> WOH-010-12	R	R	R	R	R	R	R	R	R	R	R	R	X
14	<i>Escherichia coli</i> WOH-010-13	R	S	R	R	R	S	S	S	S	S	S	R	R
15	<i>Klebsiella pneumoniae</i> WOH-010-14	R	R	R	R	R	S	R	S	S	S	S	R	R
16	<i>Escherichia coli</i> WOH-010-15	R	I	R	R	R	S	S	S	S	S	S	R	X
17	<i>Escherichia coli</i> WOH-010-16	R	R	R	R	R	S	R	R	R	R	R	R	X
18	<i>Acinetobacter baumannii</i> WOH-010-17	R	I	R	R	R	R	R	R	R	R	S	S	X
19	<i>Enterobacter cloacae</i> WOH-010-19	R	R	R	R	R	R	R	R	R	R	R	R	X
20	<i>Enterobacter cloacae</i> WOH-010-20	R	S	R	I	R	S	S	S	S	S	S	R	R
21	<i>Enterobacter cloacae</i> WOH-010-21	R	R	R	R	R	R	R	R	R	R	S	S	X
22	<i>Escherichia coli</i> WOH-010-23	R	I	R	I	S	S	S	S	S	S	S	R	X
23	<i>Enterobacter cloacae</i> WOH-010-24	R	R	R	R	R	R	R	R	R	R	R	R	X
24	<i>Escherichia coli</i> WOH-010-26	R	I	R	R	R	S	S	S	S	S	S	R	X
25	<i>Klebsiella pneumoniae</i> WOH-010-27	R	I	R	R	R	S	S	S	S	S	S	S	X
26	<i>Enterobacter cloacae</i> WOH-010-31	R	R	R	R	R	S	S	S	S	S	S	S	X
27	<i>Enterobacter cloacae</i> WOH-010-32	R	R	R	R	R	R	R	R	R	R	S	R	X
28	<i>Escherichia coli</i> WOH-010-33	R	S	R	R	I	S	S	S	S	S	S	S	X
29	<i>Escherichia coli</i> ATCC 8739	S	S	S	S	S	S	S	S	S	S	S	S	X
30	<i>Escherichia coli</i> ATCC 25922	S	S	S	S	S	S	S	S	S	S	S	S	X

I = Indeterminate, R = Resistant, S = Susceptible, X = Not detected.

Table 5. Discrepancies between QIAstat-Dx BCID GN Plus AMR Panel and antimicrobial drug susceptibility testing for Beta-lactam antibiotic class.

Antimicrobial drug susceptibility testing	QIAstat-Dx BCID GN Plus AMR Panel											
	Beta-lactamases class A group (ESBL)										Beta-lactamases class C group	
	CTX-M		GES		SHV		VEB		TEM		AmpC	
	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)
Ampicillin												
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	15 (88.2)	13 (100.0)	23 (92.0)	5 (100.0)	20 (90.9)	8 (100.0)	22 (91.7)	6 (100.0)	16 (88.9)	12 (100.0)	27 (93.1)	1 (100.0)
S	2 (11.8)	0 (0.0)	2 (8.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (8.3)	0 (0.0)	2 (11.1)	0 (0.0)	2 (6.9)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ampicillin_Sulbactam												
I	3 (17.6)	5 (38.5)	8 (32.0)	0 (0.0)	7 (31.8)	1 (12.5)	8 (33.3)	0 (0.0)	2 (11.1)	6 (50.0)	8 (27.6)	0 (0.0)
R	11 (64.7)	5 (38.5)	11 (44.0)	5 (100.0)	9 (40.9)	7 (87.5)	11 (45.8)	5 (83.3)	10 (55.6)	6 (50.0)	15 (51.7)	1 (100.0)
S	3 (17.6)	3 (23.1)	6 (24.0)	0 (0.0)	6 (27.3)	0 (0.0)	5 (20.8)	1 (16.7)	6 (33.3)	0 (0.0)	6 (20.7)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cefazolin												
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	13 (76.5)	13 (100.0)	21 (84.0)	5 (100.0)	18 (81.8)	8 (100.0)	20 (83.3)	6 (100.0)	16 (88.9)	10 (83.3)	25 (86.2)	1 (100.0)
S	2 (11.8)	0 (0.0)	2 (8.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (8.3)	0 (0.0)	2 (11.1)	0 (0.0)	2 (6.9)	0 (0.0)
X	2 (11.8)	0 (0.0)	2 (8.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (16.7)	2 (6.9)	0 (0.0)
Cefepime												
I	1 (5.9)	1 (7.7)	2 (8.0)	0 (0.0)	2 (9.1)	0 (0.0)	1 (4.2)	1 (16.7)	1 (5.6)	1 (8.3)	2 (6.9)	0 (0.0)
R	8 (47.1)	11 (84.6)	16 (64.0)	3 (60.0)	11 (50.0)	8 (100.0)	15 (62.5)	4 (66.7)	10 (55.6)	9 (75.0)	18 (62.1)	1 (100.0)
S	8 (47.1)	1 (7.7)	7 (28.0)	2 (40.0)	9 (40.9)	0 (0.0)	8 (33.3)	1 (16.7)	7 (38.9)	2 (16.7)	9 (31.0)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ceftazidime												
I	0 (0.0)	2 (15.4)	2 (8.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (8.3)	0 (0.0)	2 (11.1)	0 (0.0)	2 (6.9)	0 (0.0)
R	10 (58.8)	9 (69.2)	15 (60.0)	4 (80.0)	11 (50.0)	8 (100.0)	14 (58.3)	5 (83.3)	10 (55.6)	9 (75.0)	18 (62.1)	1 (100.0)
S	7 (41.2)	2 (15.4)	8 (32.0)	1 (20.0)	9 (40.9)	0 (0.0)	8 (33.3)	1 (16.7)	6 (33.3)	3 (25.0)	9 (31.0)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ceftazidime_Avibactam												
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	6 (35.3)	3 (23.1)	7 (28.0)	2 (40.0)	5 (22.7)	4 (50.0)	6 (25.0)	3 (50.0)	5 (27.8)	4 (33.3)	8 (27.6)	1 (100.0)
S	11 (64.7)	10 (76.9)	18 (72.0)	3 (60.0)	17 (77.3)	4 (50.0)	18 (75.0)	3 (50.0)	13 (72.2)	8 (66.7)	21 (72.4)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Piperacillin_Tazobactam												
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	7 (41.2)	5 (38.5)	9 (36.0)	3 (60.0)	6 (27.3)	6 (75.0)	8 (33.3)	4 (66.7)	6 (33.3)	6 (50.0)	11 (37.9)	1 (100.0)
S	10 (58.8)	8 (61.5)	16 (64.0)	2 (40.0)	16 (72.7)	2 (25.0)	16 (66.7)	2 (33.3)	12 (66.7)	6 (50.0)	18 (62.1)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 6. Discrepancies between QIAstat-Dx BCID GN Plus AMR Panel and antimicrobial drug susceptibility testing for Carbapenem antibiotic class.

Antimicrobial drug susceptibility testing	QIAstat-Dx BCID GN Plus AMR Panel					
	Carbapenem (class B group)			Carbapenem/Oxacillinase (class D group)		
	NDM		OXA-23		OXA-48 like	
	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)
Ertapenem						
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	4 (19.0)	9 (100.0)	11 (39.3)	2 (100.0)	11 (39.3)	2 (100.0)
S	17 (81.0)	0 (0.0)	17 (60.7)	0 (0.0)	17 (60.7)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imipenem						
I	3 (14.3)	0 (0.0)	3 (10.7)	0 (0.0)	3 (10.7)	0 (0.0)
R	2 (9.5)	9 (100.0)	9 (32.1)	2 (100.0)	9 (32.1)	2 (100.0)
S	16 (76.2)	0 (0.0)	16 (57.1)	0 (0.0)	16 (57.1)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meropenem						
I	1 (4.8)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	1 (50.0)
R	2 (9.5)	9 (100.0)	9 (32.1)	2 (100.0)	10 (35.7)	1 (50.0)
S	18 (85.7)	0 (0.0)	18 (64.3)	0 (0.0)	18 (64.3)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 7. Discrepancies between QIAstat-Dx BCID GN Plus AMR Panel and antimicrobial drug susceptibility testing for Aminoglycoside antibiotic class.

Antimicrobial drug susceptibility testing	QIAstat-Dx BCID GN Plus AMR Panel			
	Aminoglycoside-modifying resistance gene			
	<i>armA</i>		<i>aac (6')-Ib</i>	
	Neg N (%)	Pos N (%)	Neg N (%)	Pos N (%)
Amikacin				
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
R	5 (17.9)	2 (100.0)	6 (25.0)	1 (16.7)
S	23 (82.1)	0 (0.0)	18 (75.0)	5 (83.3)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gentamicin				
I	1 (3.6)	0 (0.0)	0 (0.0)	1 (16.7)
R	16 (57.1)	2 (100.0)	13 (54.2)	5 (83.3)
S	11 (39.3)	0 (0.0)	11 (45.8)	0 (0.0)
X	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Discussion

A bloodstream infection occurs when the body responds to bacteria or other diseases, causing widespread inflammation. If severe, it can lead to shock, organ failure, and a life-threatening situation. Early treatment is crucial.¹⁸ Doctors start by evaluating the patient's symptoms and performing blood cultures, which take 3 to 5 days for results. Due to the urgency, they must quickly diagnose and prescribe broad-spectrum antibiotics. Delayed or incorrect treatment increases the risk of death.¹⁹ In recent years, molecular biology methods have been employed to detect pathogens in sepsis. This has significantly reduced the detection time while showcasing excellent diagnostic performance.^{20, 21}

The evaluation of QIAstat-DX in this study revealed that it exhibited high sensitivity (91.5%), specificity (93.3%), and negative predictive value (98.5%). In contrast, the panel indicated a moderate positive predictive value (74.10%). Moreover, false negative results (8.5%) were found because EBC was not included in the panel. Based on our results, the panel performs better to detect resistant genes NDM and SHV in 4 and 3 bacterial strains, respectively (Table 1). Conventional PCR has a higher chance of giving false negatives if there are issues during the DNA extraction step.²² Moreover, a similar study shows that this panel can provide faster results than conventional PCR.²³ However, a limitation of the panel was demonstrated in our study because 2 genes of the beta-lactam groups (EBC and OXA) and 1 gene (*mcr-3*) of colistin resistance were excluded by the panel. EBC is an enzyme belonging to Class C beta-lactamases, also called AmpC beta-lactamases or cephalosporinases, which degrade drugs in the cephalosporin group. The gene responsible for producing EBC is located on the chromosome. However, it has been recently discovered that the gene can also be plasmid-located, the same as for FOX and DHA enzymes.²⁴ OXA is an enzyme belonging to Class D carbapenemases. Currently, more than 45 types of OXA-type carbapenemases have been identified.²⁵ However, the QIAstat-Dx BCID GN Plus AMR Panel can only detect specific variants, including OXA-23, OXA-48 like, OXA-24/40, and OXA-58. *mcr-3* gene, associated with colistin resistance, and is plasmid-located. Colistin is the last option for treating infections

caused by gram-negative bacteria resistant to almost all other drugs.²⁶ Our study suggested that the panel should include EBC, OXA, and *mcr-3* genes because these genes can be found in some strains of *E. cloacae*, *E. coli*, and *K. pneumoniae*.²⁷ Moreover, the genotypic detection of beta-lactamase and carbapenem genes revealed 100% determinant for a phenotypically resistant to ampicillin, ertapenem, and imipenem. In contrast, the *aac6_Ib* gene showed the lowest determinant for a phenotypically resistant to amikacin, with 16.7% (Table 7). Based on our research findings, the presence of antimicrobial resistance genes may not directly cause antibiotic resistance in the bacterial isolates we studied.²⁸

This suggests that other genes might be involved in the mechanism of antimicrobial resistance.²⁹ Although the QIAstat-Dx BCID GN Plus AMR Panel helps detect resistance genes more efficiently, we recommend additional antibiotic susceptibility tests, especially when the panel shows a negative result.³⁰ The test kit has some limitations, such as its inability to detect gram-positive bacteria causing bloodstream infections.^{31,32} Moreover, bloodstream infections can resist multiple drug groups, not just beta-lactams and aminoglycosides, but also other antibiotics like polymyxins (colistin).³³ This interpretation maintains the scientific context while making the language more accessible and straightforward for general understanding.

Conclusion

This study evaluated the QIAstat-Dx BCID GN Plus AMR Panel for its ability to detect Gram-negative bacteria and associated antimicrobial resistance genes, focusing on bloodstream infections potentially caused by environmental antibiotic-resistant bacteria. In contrast, the panel demonstrated high sensitivity and specificity, but its limitations were detecting specific key resistance genes, such as EBC, OXA, and *mcr-3*. Additionally, the bacterial isolates used in this study were not directly derived from bloodstream infections, which may impact their applicability in clinical settings. The study highlights the panel's potential to aid in rapidly diagnosing bloodstream infections caused by environmental antibiotic-resistant bacteria, though further validation with clinical

bloodstream isolates is necessary. To improve its diagnostic utility, future iterations of the panel should include a broader range of resistance genes relevant to both clinical and environmental pathogens. Complementary phenotypic antibiotic susceptibility testing remains essential, particularly in cases where the panel does not detect resistance genes.

Conflict of interest

The authors declare no conflict of interest related to this study.

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Ethical approval

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References

- [1] Jantarabenjakul W, Anugulruengkitt S, Puthanakit T, Pancharoen C. Drug-resistant bacteria: Drug-resistant organisms in pediatrics: Diagnosis and treatment. 1st Bangkok: Active Print; 2019: 288 [in Thai].
- [2] Global Database for Tracking Antimicrobial Resistance (AMR) Country Self-assessment Survey (TrACSS). Available from: <https://amrcountryprogress.org/#/download-responses>.
- [3] Tancharoen L, Pairattanakorn P, Thamlikitkul V, Angkasekwinai N. Epidemiology and burden of sepsis at Thailand's largest university-based National Tertiary Referral Center during 2019. *Antibiotics*. 2022 Jul 5;11(7):899.
- [4] Phumart P, Phodha T, Thamlikitkul V, Riewpaiboon A, Prakongsai P, Limwattananon S. Health and economic impacts of antimicrobial resistant infections in Thailand: A preliminary study. *J Health Syst Res*. 2012; 6(3): 352-60 (in Thai).
- [5] Indrawattana N, Vanaporn M. Nosocomial infection. *J Med Health Sci*. 2015; 22(1): 81-92.
- [6] Thawornwan U, Kongsanan P, Chaisukda S, Eampokalap B. Incidence of AmpC β -lactamase producing bacteria isolated in Bamrasnaradura Infectious Disease Institute during July-September 2007. *J Bamrasnaradura Infect Dis Inst*. 2007; 2(1): 32-9 (in Thai).
- [7] Wongut-sa P. Extended-spectrum β -Lactamases producing in *Escherichia coli* and *Klebsiella pneumoniae* isolated from specimens of patients in Ratchaburi Hospital (2009-2013). *J Med Public Health Region 4*. 2013; 17(3): 222-9 (in Thai).
- [8] Shanthi M, Sekar U, Arunagiri K, Sekar B. Detection of Amp C genes encoding for beta-lactamases in *Escherichia coli* and *Klebsiella pneumoniae*. *Indian J Med Microbiol*. 2012; 30(3): 290-5. doi: 10.4103/0255-0857.99489.
- [9] Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018; 4(3): 482-501. doi: 10.3934/microbiol.2018.3.482.
- [10] Rabaan AA, Eljaaly K, Alhumaid S, Albayat H, Al-Adsani W Sabour AA, et al. An overview on phenotypic and genotypic characterisation of carbapenem-resistant Enterobacterales. *Medicina*. 2022; 58(11): 1675. doi: 10.3390/medicina58111675.
- [11] Gharaibeh MH, Shatnawi SQ. An overview of colistin resistance, mobilized colistin resistance genes dissemination, global responses, and the alternatives to colistin: A review. *Vet World*. 2019; 12(11): 1735-46. doi: 10.14202/vetworld.2019.1735-1746.
- [12] Doi Y, Wachino JI, Arakawa Y. Aminoglycoside Resistance: The emergence of acquired 16S Ribosomal RNA methyltransferases. *Infect Dis Clin North Am*. 2016; 30(2): 523-37. doi: 10.1016/j.idc.2016.02.011.
- [13] Banerjee R, Patel R. Molecular diagnostics for genotypic detection of antibiotic resistance: current landscape and future directions. *JAC Antimicrob Resist*. 2023; 5(1): dlad018. doi.org/10.1093/jacamr/dlad018.
- [14] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 34th CLSI supplement M100. Wayne: CLSI; 2024.
- [15] European Committee on Antimicrobial Susceptibility Testing. Antimicrobial susceptibility testing. 2024 [cited 2024 Nov 4]. Available from: https://www.eucast.org/ast_of_bacteria.
- [16] European committee on antimicrobial susceptibility testing. La Société française de microbiologie (SFM) guidelines. 2024 [cited 2024 Nov 4]. Available from: <https://www.eucast.org/>.
- [17] Ruekit S, Srijan A, Serichantalergs O, Margulieus KR, Mc Gann P, Mills EG, et al. Molecular characterization of multidrug-resistant ESKAPEE pathogens from clinical samples in Chonburi, Thailand (2017-2018). *BMC Infect Dis*. 2022; 22(1): 695. doi: 10.1186/s12879-022-07678-8.
- [18] Kiattimanaroj A. The development of a model of care for patients with sepsis, Wapipathum Hospital. *Acad J Mahasarakham Provincial Public Health Office*. 2021; 5(9): 27 (in Thai).
- [19] Maenchantrarath C. Detection of bacteria in blood using the Bactec™FX: Procedure manual. Sparks: Becton Dickinson and Company; 2020.
- [20] Sun J, Zhao S, Wei C, Liu J, Chen J, Xing L, et al. A diagnostic test of real-time PCR detection in the diagnosis of clinical bloodstream infection. *Ann Palliat Med*. 2022; 11(10): 3224-30. doi: 10.21037/apm-22-1071.
- [21] Trung NT, Thau NZ, Bang MH, Song LH. PCR-based sepsis@Quick test is superior in comparison with blood culture for identification of sepsis-causative pathogens. *Sci Rep*. 2019; 9(1): 13663. doi: 10.1038/s41598-019-50150-y.
- [22] Department of Disease Control. Thailand's integrated antimicrobial resistance surveillance with One Health Approach guideline. Nonthaburi: Ministry of Public Health; 2019: 112.
- [23] Roschanski N, Fischer J, Guerra B, Roesler U. Development of a multiplex real-time PCR for the

- rapid detection of the predominant beta-lactamase genes CTX-M, SHV, TEM and CIT-Type AmpCs in Enterobacteriaceae. PLoS ONE. 2014; 9(7): e100956. doi.org/10.1371/journal.pone.0100956.
- [24] Thummeepak R, Kongthai P, Leungtongkam U, Sitthisak S. Distribution of virulence genes involved in biofilm formation in multi-drug resistant *Acinetobacter baumannii* clinical isolates. Int Microbiol. 2016; 19(2): 121-9. doi: 10.2436/20.1501.01.270.
- [25] Juntanawiwat P, Thunyaharn S, Visawapoka U, Samosornsuk W, Samosornsuk S. The prevalence of OXA-type genes in carbapenem-resistant *Acinetobacter baumannii* isolated from critically ill patients in the intensive care unit of Phramongkutklao Hospital. J Med Tech Phys Ther. 2016; 28(2): 120-8.
- [26] Wongut-sa P, Khumdee P, Samosornsuk W, Yansombat J, Samosornsuk S. Prevalence of colistin resistance among third-generation cephalosporins- or carbapenem-resistant enterobacteriaceae Isolated from clinical specimens in Ratchaburi Hospital, Thailand. J Med Tech Assoc Thailand. 2020; 48(1): 60 (in Thai).
- [27] Ku YH, Lee MF, Chuang YC, Yu WL. Detection of plasmid-mediated β -lactamase genes and the emergence of a novel AmpC (CMH-1) in *Enterobacter cloacae* at a Medical Center in Southern Taiwan. J Clin Med. 2019; 8(1): 8. doi: 10.3390/jcm8010008.
- [28] Department of Medical Services, Health Systems Research Institute. EE-AMR Tool Thailand. 2021 [cited 2024 Nov 4]. Available from: <https://kb.hsri.or.th/dspace/handle/11228/5684>.
- [29] Swe-Han K, Pillay M. Amikacin-resistant *Acinetobacter* species mediated by the *aphA6* gene associated with clinical outcome at an academic complex hospital in KwaZulu-Natal Province. S Afr Med J. 2020; 110(1): 49-54. doi.org/10.7196/samj.2020.v110i1.14045.
- [30] Abouelfetouh A, Torky AS, Aboulmagd E. Phenotypic and genotypic characterization of carbapenem-resistant *Acinetobacter baumannii* isolates from Egypt. Antimicrob Resist Infect Control. 2019 Dec;8(1):185. doi.org/10.1186/s13756-019-0611-6.
- [31] Ramachandran G. Gram-positive and gram-negative bacterial toxins in sepsis. Virulence. 2014; 5(1): 213-8. doi: 10.4161/viru.27024.
- [32] Wang Q, Li X, Tang W, Guan X, Xiong Z, Zhu Y, et al. Differential Gene Sets Profiling in Gram-Negative and Gram-Positive Sepsis. Front Cell Infect Microbiol. 2022 Feb 9;12:1-11. doi.org/10.3389/fcimb.2022.801232.
- [33] Olaitan A, Morand S, Rolain JM. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front Microbiol. 2014; 5: 643. doi: 10.3389/fmicb.2014.00643.

Relationship between sit-to-walk performance and visual perception in children with typical development: A preliminary study

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ABSTRACT

Background: Performance of sit-to-walk (STW) is developed along with improvement in neuromuscular control. Visual development plays an important role for motor learning and function in childhood. There was little evidence to indicate the relationship between visual function and motor performance.

Objective: This study aims to examine the relationship between STW performance and visual perception in children with typical development.

Materials and methods: Fifteen healthy children aged 7 to 12 years participated in the study. They were asked to complete the Development Test of Visual Perception-Third Edition (DTVP-3). Motion capture was used to collect spatiotemporal data from five STW trials. The relationship between these spatiotemporal parameters and visual perceptual scores were analyzed by the Pearson correlation coefficient.

Results: Positive moderate and high correlation were found between the eye-hand coordination sub-score and the first ($r=0.52$, $p<0.05$) and second step width ($r=0.71$, $p<0.01$) of STW, respectively. The second step width also correlated with the visual-motor integration composite ($r=0.55$, $p<0.05$). There was moderate correlation between the stride length and the copying subtest ($r=0.52$, $p<0.05$).

Conclusion: This preliminary study demonstrated that some spatial parameters of STW performance were associated with the visual-motor abilities of the DTVP-3. This suggested that an improvement in motor performance is developed along with visual perceptual function especially motor involving task.

Introduction

Sit-to-walk (STW) is a combined movement between sit-to-stand (STS) and gait initiation (GI). The performance of this transition is affected by age. In older adults, ability to achieve STW relates to the deterioration of physical, physiological, and psychological systems.¹ In contrast, children begin to perform this action at the age of 3 years.² They require greater control and coordination of neuromuscular systems to complete complex movements including STW since these functions are not fully developed.³ With increasing age, better performance of motor control is particularly associated with the improvements of sensory functions, perception, and integration, especially the visual system.⁴

Visual development is important in the improvement of motor control during childhood.⁵ It allows children to learn and engage with the environment which, enhances their movement skills. Information that is perceived from vision is integrated into motor planning. It also provides

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visual feedback that helps individuals to improve their movement performance.⁴ This visual-motor process requires children to recognize, organize, and interpret visual information which is called visual perception. This cognitive function is commonly correlated with reading comprehension and fine motor skills.⁶ A highly positive correlation between each component of visual perception and gross motor skills has been demonstrated in children aged 5 years. The study suggested that therapists should assess this cognitive skill in typically developing children because it may be beneficial in optimizing their movement performance.⁷

The evaluation of visual perception involves activity measurements that require motor ability and motor-free response.⁸ Eye-hand coordination, such as drawing and copying, is the task that reflect visual perceptual involving motor activities. Motor-free visual perception is the ability to recognize objects or words, which is considered a pure form of visual perception, for instance, form constancy and position in space.⁹ These perceptions have been correlated with gross motor skills including, locomotion and hand functions. However, the study focused on the movement process rather than performance outcomes.⁷ Generally, spatiotemporal parameters are used to indicate movement performance. Clarifying that visual perception development is associated with better gross motor performance requires an investigation of the link between these capabilities in school-aged children.

STW is often included in daily activities of individuals but, its performance was rarely be interested.¹⁰ Considering on each component of STW, it has been suggested that visual perception is important for balance control during STS as well as step length of GI in young healthy adults.^{11, 12} Since STW is more complex and it develops in children along with their visual perceptual skills, the objective of this preliminary study was to examine the relationship between STW performance and visual perception in children with typical development (TD). Total movement time, step length, stride length, and step width were calculated to indicate the performance of STW. For visual perception skills, the performance of each ability can be used to indicate strength and weakness of individual.¹³ The correlation of STW parameters with scores of each subtest and composite index of visual perception was determined. Researchers hypothesized that, in children with TD, visual perception would be correlated with spatiotemporal characteristics of STW performance.

Materials and methods

This cross-sectional correlational study was conducted to gather spatiotemporal data of STW performance and visual perceptual level. These data were examined for correlations.

Participants

The sample size was calculated based on the expected correlation coefficient at 0.70 ($\alpha=0.05$, $\beta=0.20$) with considering 10% of dropout rate. This preliminary

study included 15 convenience participants who were healthy children with TD aged 7 to 12 years old (seven boys and eight girls) from the Bangkok metropolitan region. Their means and standard deviations of age, weight, and height were 9.1 ± 1.6 years, 32.05 ± 9.16 kg., and 1.35 ± 0.11 m., respectively. These children were able to perform expecting child-level activities without reporting of cognitive, emotional, and academic problems from their parents.¹⁴ They had no history of surgery or fracture of the trunk or lower limb regions in the past 6 months or visual impairment. Informed consent was obtained from the parent or guardian of each participant. Participants who were unable to complete the testing protocol were allowed to withdraw from the study at any time. However, there was no withdrawal in this study.

Instruments

Three-dimensional (3D) motion analysis system (Motion Analysis Corporation, Santa Rosa, CA, USA) with 8 motion-capture cameras (Raptor E) and motion analysis software (Cortex, version 8.1 and KinTools RT, version 2.0, Motion Analysis Corporation, Santa Rosa, CA, USA) were used to calculate spatiotemporal data. An adjustable chair was used to set the chair height specific to each participant. The Development Test of Visual Perception - Third Edition (DTVP-3) was selected to assess visual perceptual skills. This test was developed to measure both motor-enhanced and motor-reduced abilities. The DTVP-3 has shown its reliability and validity in children with TD aged 4 to 12 years old.⁹ It consists of 5 subtests: eye-hand coordination (EH), copying (CO), figure-ground (FG), visual closure (VC), and form constancy (FC). These subtests are construction of visual perception which indicates the different dimensions of this cognitive skill.¹⁵ The scores from the EH and CO subscales were used to calculate the visual-motor integration (VMI) index, and the rest (FG, VC, and FC) were summed to evaluate the motor-reduced visual perception (MRVP) composition. The sum of the overall scores was converted into the general visual perception (GVP). The difference of these composite indexes was used to indicate that the children encountered with visual perceptual difficulty or they actually had motor deficits.¹³ Each subtest and composite index score were interpreted using the descriptive meanings of the test which presented in Table 1.

Table 1. Descriptive terms of subtest and composite index score of the DTVP-3.

Subtest score	Descriptive terms	Composite score
1-3	Very poor	<70
4-5	Poor	70-79
6-7	Below average	80-89
8-12	Average	90-110
13-14	Above average	111-120
15-16	Superior	121-130
17-20	Very superior	>130

Procedure

The overall testing processes were done by a pediatric physical therapist who is familiar with both DTVP-3 and 3D-motion capture. The demographic data, comprising date of birth, gender, weight, and height were collected at the enrolment. Weight and height were used to calculate body mass index (BMI) based on BMI chart for Thai Children from the Thai Society for Pediatric Endocrinology. The participants were asked to individually complete the DTVP-3 under instruction from the tester. They were then requested to wear a vest and shorts without shoes. Reflexive markers were attached on 29 anatomical landmarks based on the Modified Helen Hayes marker set model. Two additional markers were placed on the adjustable chair and another one at the right greater trochanter for identifying the point of seat-off.¹⁶ The intrasubject and test-retest reliability of the marker placements done in the laboratory prior data collection were demonstrated between good to excellent level ($R=0.846-0.982$, and $0.772-0.967$, respectively). The participants then sat on the chair, which was adjusted in height according to the length of their lower leg with 25% of upper-leg length support, and feet at the shoulder width apart. These settings allowed the hip and knee joints to be flexed close to 90° , as well as ankle dorsiflexion. From the starting position, the participants were instructed to stand and walk toward the end of the walkway approximately 3 meters away with their preferred speed and pattern. They were allowed to practice before data collection to familiarize themselves with the task and environment. The spatiotemporal data from five completed STW trials were used for further analysis.

Data processing and interpretation

Spatiotemporal data comprising total movement time, step length, stride length and step width were computed by using KinTool RT (version 2.0, Motion Analysis Corporation, Santa Rosa, CA, USA). Total movement time was determined from the point that the velocity of the body movement was 0.01 m/s to the first contact of the stance limb. The step length was calculated by the distance between two markers on both heels in the anteroposterior axis, and the step width was measured in the mediolateral direction. The stride length was determined by the distance between the points of initial contact of the marker on the stance heel. For the visual perceptual skills, the scores of each subtest and composite index were used to determine the level of these abilities using the descriptive meanings shown in Table 1.

Data analysis

Descriptive statistics were used to characterize the spatiotemporal data and visual perception scores. The Shapiro-Wilk test indicated a normally distribution of both data sets. Since each subtest and composite index of the DTVP-3 demonstrated the different dimensions of visual perceptual skills, these scores were used to evaluate the correlation with each spatiotemporal parameter by the

Pearson correlation coefficient (r). The findings were translated into the interpretation descriptions.¹⁷

Results

Spatiotemporal parameters

The means and standard deviations (SD) of total movement time, first and second step length, first and second step width, and stride length shown in Table 2. The mean of the first step length was similar to the second, whereas the mean of second step width was narrower than the first.

Table 2. Mean $\pm$ SD of spatiotemporal parameters.

Parameters	Mean $\pm$ SD
Total movement time (sec)	2.06 $\pm$ 0.19
1 st Step length (cm)	47.37 $\pm$ 5.49
2 nd Step length (cm)	48.62 $\pm$ 8.90
Stride length (cm)	96.00 $\pm$ 13.87
1 st Step width (cm)	12.53 $\pm$ 3.50
2 nd Step width (cm)	8.31 $\pm$ 2.73

Visual perceptual scores

The means and SD of each subtest and composite index of the DTVP-3 are shown in Table 3. The mean scores of the EH, FG, and FC subtests and MRVP index were at average levels. The means of the VC subscale and GVP index were above average level. The average VMI index was at the superior level, and the CO subtest was at the very superior level.

Table 3. Mean $\pm$ SD of each subtest and composite index scores.

DTVP-3	Scores
Subtest	
: EH	10.60 $\pm$ 2.63
: CO	18.13 $\pm$ 2.47
: FG	8.87 $\pm$ 1.82
: VC	13.87 $\pm$ 2.63
: FC	10.33 $\pm$ 4.70
Composite index	
: VMI	126.00 $\pm$ 12.38
: MRVP	106.07 $\pm$ 15.54
: GVP	115.33 $\pm$ 12.74

Relationship between spatiotemporal parameters and visual perceptual skills

The correlation between spatiotemporal parameters and visual perceptual scores are shown in Table 4. Positive moderate correlations with statistical significance were found between stride length and CO subtest, first step width and the EH subtest, and second step width and the VMI index. The second step width also demonstrated a highly positive correlation with the EH subtest.

Table 4 Correlation between spatiotemporal parameters and each subtest and composite index score.

Spatiotemporal parameters	DTVP-3							
	Subtests					Composite indexes		
	EH	CO	FG	VC	FC	VMI	MRVP	GVP
1 st SL	0.23	0.51	0.12	0.16	-0.19	0.44	-0.04	0.16
2 nd SL	0.13	0.49	0.17	0.23	-0.19	0.37	-0.01	0.15
StrL	0.17	0.52*	0.16	0.21	-0.20	0.41	-0.02	0.16
1 st SW	0.52*	-0.01	-0.35	-0.49	-0.05	0.34	-0.29	-0.09
2 nd SW	0.71**	0.14	-0.12	0.07	0.37	0.55*	-0.23	0.38
TMT	0.02	0.21	0.33	0.06	0.16	0.14	0.19	0.21

Note: TMT: total movement time, SL: step length, StrL: stride length, SW: step width, EH: eye-hand coordination, CO: copying, FG: figure-ground, VC: visual closure, FC: form constancy, VMI: visual-motor integration, MRVP: motor-reduced visual perception, GVP: general visual perception, * $p < 0.05$, ** $p < 0.01$

Discussion

The relationship between STW performance and visual perception was examined in children with TD aged between 7 and 12 years. A moderate to high positive correlation was demonstrated between some spatial parameters and visual-motor integration dimensions. The results suggested that some parameters of movement are associated with the development of some visual perceptual skills in typically developing children.

The current findings showed moderate and high positive correlations between the first and second step width and the EH subtest ($r = 0.52$, $p < 0.05$ and $r = 0.71$, $p < 0.01$, respectively). Generally, eye-hand coordination relates to hand functions, but it is actually part of the visual-motor coordination that also connects with gross motor activities.¹⁸ This skill requires the ability of the motor system to control movement in relation to visual information without the action of an integrative process.¹⁹ During STW, the base of support (BOS) of individuals was narrower from the starting position. The average first step width was greater than the second. This result is similar to a study of gait analysis that focused on the first four steps of GI.²⁰ It could be explained by the sudden change of the BOS from double- to single-leg contact at the initiation of walking. Participants could maintain their balance by appropriate coordination between the eyes and lower limb movement since the mean score of the EO subtest was at an average level. The second step width also had a moderate correlation with the VMI composition ($r = 0.55$, $p < 0.05$). Since the average of this score was at superior level, this allowed the participants to integrate visual information from the surrounding environment before performing the next action.¹⁹ Consequently, the second step width was narrower, which similar to a study of gait parameters in children aged 2 to 17 years.²¹

A moderate positive correlation was found between the stride length and the CO skill in the current study ($r = 0.52$, $p < 0.05$). Copying is the ability to recognize words or objects and then express them by spelling, writing, or drawing. To reproduce these actions, children must recall specific information from their immediate or long-term visual-spatial memory.²² Speed and accuracy are commonly used to measure the ability of this cognitive function.²³ The CO scores of the participants in this study demonstrated

that their copying skills ranged between average and very superior levels. This indicates good collaboration between working memory and motor outcomes. Although this current study did not provide any visual information related to STW performance to the participants, they reproduced the appropriate stride length from their long-term memory, which may particularly be relevant to their daily walking.

The relationship between these spatial parameters and visual perception involving motor abilities during STW performance may relate to the movement segmentation. STW is a combination of STS, which is the primary movement, and GI. The first segment of movement is proposed to be controlled by motor planning processes, whereas the secondary action is corrected by visual feedback.²⁴ Visual feedback allows individuals to recognize their body position while performing the movement. In a rapid situation, the motor response could be associated with the movement time since the action was performed without the integration of visual information.²⁵ However, weak correlations existed between total movement time and all subscales of visual perception in the current study. This could be because the participants performed this transition with their preferred speed and pattern. They may have fluently initiated their gait while the body was not in the upright position or started to walk after quiet standing (sit-to-stand-and-walk). Therefore, movement time was not constrained, which allowed the participants to use visual feedback to integrate information before they initiated the walk.

The findings in the current study did not demonstrate the relationship between STW performance and all of MRVP scores. These different from the previous study which found moderate to high correlation between gross motor skills and all of visual perceptual abilities except the position in space item.⁷ Although motor-free visual perceptual constructs were necessary for VMI skills, these MRVP abilities were only correlated with motor performance which particularly required speed for action.^{8, 26}

The limitation of the study is small sample size which would not determine the correlation between STW performance and visual perception in overall population of children. It has been suggested that visual perceptual level

in children with TD also related with their socioeconomic status.²⁷ Further study requires larger number of children with the different of socioeconomic status since this factor affects on visual perception outcomes. Furthermore, as the same tester completed the DTVP-3 and 3d-motion capture, tester bias may also exist. Consequently, in order to assist with future research, additional testers might be needed.

Conclusion

This preliminary study demonstrated the relationship between spatial parameters of STW performance including step widths and stride length, and visual perception skills which require motor involvement in children with TD. The moderate to high positive correlation suggests that the development of visual perceptual skills, especially integrative visual-motor functions particularly influence the performance of movement. Involving visual perceptual activities in the classroom and daily life would be beneficial to promote movement performance in school-aged children.

Conflict of interest

The authors declare no conflict of interest in this study.

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Ethical Approval

This study was approved by The Research Ethics Review Committee for Research Involving Human Research Participants, Group I, Chulalongkorn University (COA No. 144/66).

References

- [1] Perera CK, Gopalai AA, Gouwanda D, Ahmad SA, Nurzaman SG. A review on sit-to-walk biomechanics for healthy young and older adults. In 7th IEEE-EMBS Conference on Biomedical Engineering and Sciences, IECBES 2022 - Proceedings. IEEE, Institute of Electrical and Electronics Engineers. 2022. p. 17-22 doi: 10.1109/IECBES54088.2022.10079546.
- [2] Nicolini-Panisson RD, Donadio MV. Timed "Up & Go" test in children and adolescents. *Rev Paul Pediatr*. 2013; 31(3): 377-83. doi: 10.1590/S0103-05822013000300016.
- [3] Prebor J, Samulski B, Armitano-Lago C, Morrison S. Patterns of movement performance and consistency from childhood to old age. *Motor Control*. 2023; 27(2): 258-74. doi: 10.1123/mc.2022-0006.
- [4] Shafer RL, Solomon EM, Newell KM, Lewis MH, Bodfish JW. Visual feedback during motor performance is associated with increased complexity and adaptability of motor and neural output. *Behav Brain Res*. 2019; 376: 112214. doi: 10.1016/j.bbr.2019.112214.
- [5] Sánchez-González MC, Palomo-Carrión R, De-Hita-Cantalejo C, Romero-Galisteo RP, Gutiérrez-Sánchez E, Pinero-Pinto E. Visual system and motor development in children: a systematic review. *Acta Ophthalmol*. 2022; 100(7): e1356-e69. doi: 10.1111/aos.15111.
- [6] Bellocchi S, Muneaux M, Huau A, Lévêque Y, Jover M, Ducrot S. Exploring the link between visual perception, visual-motor integration, and reading in normal developing and impaired children using DTVP-2. *Dyslexia*. 2017; 23(3): 296-315. doi: 10.1002/dys.1561.
- [7] Tepeli K. The relationship between gross motor skills and visual perception of preschoolers. *TJSE*. 2014; 15(1): 43-53. doi:10.15314/tjse.35867.
- [8] Brown T. Are motor-free visual perception skill constructs predictive of visual-motor integration skill constructs? *Hong Kong J Occup Ther*. 2012; 22(2): 48-59. doi:10.1016/j.hkjot.2012.06.003.
- [9] Brown T. Validity and Reliability of the Developmental Test of Visual Perception - Third Edition (DTVP-3). *Occup Ther Health Care*. 2016; 30(3): 272-88. doi: 10.3109/07380577.2015.1136757.
- [10] Jones GD, James DC, Thacker M, Green DA. Parameters that remain consistent independent of pausing before gait-initiation during normal rise-to-walk behaviour delineated by sit-to-walk and sit-to-stand-and-walk. *PLoS One*. 2018; 13(10): e0205346. doi: 10.1371/journal.pone.0205346.
- [11] Siriphorn A, Chamonchant D, Boonyong S. The effects of vision on sit-to-stand movement. *J Phys Ther Sci*. 2015; 27(1): 83-6. doi: 10.1589/jpts.27.83.
- [12] Kimijanová J, Hirjaková Z, Bzdúšková D, Hlavačka F. Influence of vision on gait initiation and first step kinematics in young and older adults. *Physiol Res*. 2021; 70(S3): S409-s17. doi: 10.33549/physiolres.934813.
- [13] Hammill D, Pearson N, Voress J. Developmental test of visual perception-Third Edition. Austin, TX: Pro-Ed; 2014.
- [14] Selman SB, Dilworth-Bart JE. Routines and child development: A systematic review. *JFTR*. 2024; 16(2): 272-328. doi: 10.1111/jftr.12549.
- [15] Harris M, Franzsen D, de Witt P. Relevance of norms and psychometric properties of three standardised visual perceptual tests for children attending mainstream schools in Gauteng. *S Afr Jo Occup Ther*. 2021; 51: 4-13. doi: 10.17159/2310-3833/2021/vol51n3a2.
- [16] Suriyaamarit D, Boonyong S. Reliability and minimal detectable change of sit-to-stand kinematics and kinetics in typical children. *Human Movement*. 2018; 19: 48-54. doi: 10.5114/hm.2018.76079.
- [17] Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate use and interpretation. *Anesthesia & Analgesia*. 2018; 126(5): 1763-8. doi: 10.1213/ANE.0000000000002864.
- [18] Orhan I. An investigation of hand-eye coordination, attention, balance and motor skill in school. *Children*. 2018; 11-8 p. doi: 10.15405/epsbs.2018.06.02.2.
- [19] Oberer N, Gashaj V, Roebbers CM. Executive functions,

- visual-motor coordination, physical fitness and academic achievement: Longitudinal relations in typically developing children. *Hum Mov Sci.* 2018; 58: 69-79. doi: 10.1016/j.humov.2018.01.003.
- [20] Muir BC, Rietdyk S, Haddad JM. Gait initiation: the first four steps in adults aged 20-25 years, 65-79 years, and 80-91 years. *Gait Posture.* 2014; 39(1): 490-4. doi: 10.1016/j.gaitpost.2013.08.037.
- [21] Gill SV, Keimig S, Kelty-Stephen D, Hung Y-C, DeSilva J. The relationship between foot arch measurements and walking parameters in children. *BMC Pediatrics.* 2016: article No.15. doi: 10.1186/s12887-016-0554-5.
- [22] Fastame MC. Visual and spatial working memory skills implicated in copying and drawing from memory of the Rey-Osterrieth complex figure: What relationship in school-aged children? *Cogn Dev.* 2020; 53: article number 100826. doi: 10.1016/j.cogdev.2019.100826.
- [23] Re AM, De Vita F, Cornoldi C, Schmidt S. Copy skills and writing abilities in children with and without specific learning disabilities. *J Learn Disabil.* 2023; 56(5): 410-20. doi: 10.1177/00222194231157089.
- [24] Wu J, Chan JSY, Yan JH. Movement segmentation and visual perturbation increase developmental differences in motor control and learning. *Dev Sci.* 2019; 22(4): e12789. doi: 10.1111/desc.12789.
- [25] Schenk T, Schindler I, McIntosh RD, Milner AD. The use of visual feedback is independent of visual awareness: evidence from visual extinction. *Exp Brain Res.* 2005; 167(1): 95-102. doi: 10.1007/s00221-005-0027-9.
- [26] Tsai C-L, Wu S-K. Relationship of visual perceptual deficit and motor impairment in children with developmental coordination disorder. *Percept Mot Skills.* 2008; 107(2): 457-72. doi: 10.2466/pms.107.2.457-472.
- [27] Abaoğlu H, Kashefimehr B, Katırcıbaşı G, Aki E. Visual Perception Skills Among Children of Different Socioeconomic Status. 2018; 6(1): 11-6. doi: 10.30720/ered.382574.

Case Report : Hemoglobin H disease caused by compound heterozygosity for α^0 -thalassemia Lamphun deletion and α^+ -thalassemia 3.7 kb deletion ($--^{Lamphun}/-\alpha^{3.7}$) in a Thai elderly case

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ABSTRACT

We report the deletional HbH disease caused by compound heterozygosity for α^0 -thalassemia Lamphun type deletion and α^+ -thalassemia 3.7 kb deletion ($--^{Lamphun}/-\alpha^{3.7}$) in a Thai elderly (61-year-old) subject. She was seen by her physician for fatigue and dyspnea. A physical examination revealed that she was a slightly pale patient. A complete blood cell count (CBC) showed microcytic hypochromic anemia (Hb 91 gm/L, MCV 73.0 fL, and MCH 21.0 pg). However, she had no history of receiving a blood transfusion. Thus, a better understanding of the genotype, phenotype, and hematological and clinical features of this HbH disease ($--^{Lamphun}/-\alpha^{3.7}$) will be helpful in treatment, genetic counseling, prevention, and control programs of thalassemia in Thailand.

Introduction

α -thalassemia is a hereditary blood disorder characterized by the impaired production of α -globin chains, vital hemoglobin components. This condition arises from mutations, especially the deletions of *HBA1* and *HBA2* genes located on chromosome 16. The α -globin chains are essential for the proper formation and function of hemoglobin (Hb), and their deficiency leads to a range of clinical manifestations, from mild anemia to severe, and life-threatening conditions. Clinically, α -thalassemia presents a spectrum of severity depending on the number and type of α -globin gene deletions.¹ The condition is classified into several forms, including α^+ -thalassemia trait ($-\alpha/\alpha$), α^0 -thalassemia trait ($--/\alpha$), HbH disease ($-\alpha/-$), and the most severe form, Hb Bart's hydrops fetalis ($--/--$). Each form presents unique clinical challenges and management needs. For instance, individuals with HbH disease may experience moderate to severe anemia and require regular monitoring and intervention. At the same time, those with Hb Bart's hydrops fetalis face a high risk of perinatal death without intrauterine interventions.²

The α^0 -thalassemia Southeast Asian ($--^{SEA}$) deletion accounted for 98% of the Thai samples with HbH disease, while the α^0 -thalassemia Thai ($--^{THAI}$) deletion made up the rest. Additionally, a 3.7 kb deletion accounted for 91% of α^+ -thalassemia, with a 4.2 kb deletion comprising the remainder of the deletional HbH disease. Meanwhile, the

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Hb Constant Spring (CS, *HBA2*: c.427T>C) variant was the predominant form of non-deletional HbH disease.³ To date, there are over 200 different mutations associated with α -thalassemia.⁴ Recently, studies conducted in Thailand have demonstrated the use of next-generation sequencing (NGS) to identify a rare mutation essential for disease prevention and control. The α^0 -thalassemia Chiang Rai ($--^{CR}$) deletion, a 44.6 kb deletion on chromosome 16, was observed in Hb Bart's hydrops fetalis in combination with $--^{SEA}$, thus completely removing both *HBA1* and *HBA2* genes.⁵ Subsequently, this mutation was identified in several unrelated cases of deletional and non-deletional HbH diseases.⁶ Moreover, a 27.0 kb deletion and a small insertion of 9 bp (CGGGAGGGA) within the α -globin gene cluster (NC_000016.10:g.158985_186051delinsCGGGAGGGA), named α^0 -thalassemia Lamphun ($--^{Lamphun}$) deletion, was reported in a 2-year-old Thai boy diagnosed with uncommon deletional HbH disease ($--^{Lamphun}/-\alpha^{3.7}$). The causative α -thalassemia alleles were inherited from his mother ($--^{Lamphun}/\alpha\alpha$) and father ($-\alpha^{3.7}/\alpha\alpha$).⁷

Case Report

In this study, the authors report the discovery of deletional HbH disease caused by compound heterozygosity for $--^{Lamphun}/-\alpha^{3.7}$ in an elderly case. She is a 61-year-old Thai woman living in Lamphun, a province in northern Thailand, who a physician saw at a private hospital for fatigue and dyspnea. Upon examination, she appeared pale and did not have hepatosplenomegaly. In 2018, she was diagnosed with colon cancer and underwent 12 cycles of chemotherapy. However, she had never received a blood transfusion. A complete blood count (CBC) was analyzed using an automated blood counter (Sysmex KX-21, Sysmex Corporation, Kobe, Japan). Laboratory findings are as follows: RBC 4.3×10^{12} cells/L, Hb 91 gm/L, PCV 0.32 L/L, MCV 73.0 fL, MCH 21.0 pg, MCHC 29.0 gm/L, and RDW 20.5%. Due to the low levels of Hb, MCV, and MCH, combined with a high level of RDW, she was

diagnosed with microcytic hypochromic anemia. However, iron deficiency anemia could be excluded because her serum iron (SI=135 μ g/dL) and total iron-binding capacity (TIBC=188 μ g/dL) were within normal values. In contrast, her serum ferritin (SF=2,865 μ g/L) was higher than the normal range. Therefore, her blood sample was sent to the Associated Medical Sciences-Clinical Service Center (AMC-CSC), Chiang Mai University, Chiang Mai Province, Thailand, for thalassemia diagnosis. In the thalassemia laboratory, hemoglobin analysis was performed using capillary electrophoresis (CE, Capillarys 2 Flex Piercing, Sebia, Norcross, Georgia). The peaks of HbH (16.1%), Hb Bart's (0.6%), and a low level of HbA₂ (0.7%) were found on the CE electropherograms (Figure 1). Thus, deletional HbH disease was suspected, and molecular analysis for the diagnosing of α -thalassemia was performed. Genomic DNA was extracted from the blood sample using the NucleoSpin® kit (Macherey-Nagel, KG., Duren, Germany) following the manufacturer's instructions. A single-tube multiplex real-time PCR with EvaGreen and high-resolution melting (HRM) analysis for the diagnosis of α^0 -thalassemia $--^{SEA}$, $--^{THAI}$, and $--^{CR}$ deletions was performed as described previously (8). Furthermore, as previously described, a multiplex gap-PCR was performed to detect α^+ -thalassemia- $\alpha^{3.7}$ and $-\alpha^{4.2}$ kb deletions.⁷ The single-tube multiplex real-time PCR with EvaGreen and HRM analysis showed a negative result for α^0 -thalassemia $--^{SEA}$, $--^{THAI}$, and $--^{CR}$ deletions, while the multiplex gap-PCR revealed a positive result for α^+ -thalassemia $-\alpha^{3.7}$ kb deletion. As described previously, conventional gap-PCR was further performed to detect α^0 -thalassemia $--^{Lamphun}$ deletion.⁷ The PCR product of approximately 1.2 kb, specific for α^0 -thalassemia $--^{Lamphun}$ deletion, was revealed (Figure 2). Based on these results, she was diagnosed with deletional HbH disease caused by compound heterozygosity for α^0 -thalassemia Lamphun deletion and α^+ -thalassemia 3.7 kb deletion ($--^{Lamphun}/-\alpha^{3.7}$).

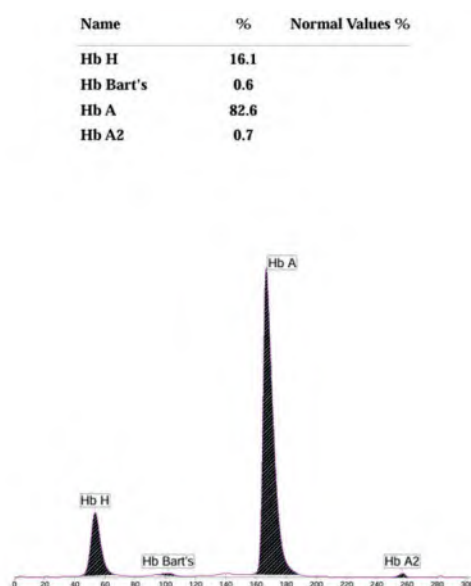


Figure 1. The CE electropherogram of the case.

Discussion

Nowadays, there are over 200 different mutations associated with α -thalassemia, and at least 20 types of α^0 -thalassemia deletion have been described.^{2,4} However, many deletions remain unknown and cannot be identified using conventional techniques. These unknown α -thalassemia deletions can pose a risk of misdiagnosis, leading to conditions such as Hb Bart's hydrops fetalis and HbH disease. In the previous study, we characterized a new 27.0 kb deletion with a small insertion of 9 bp (CGGGAGGGA) in the α -globin gene cluster, spanning both the *HBA1* and *HBA2* genes. This mutation was named α^0 -thalassemia Lamphun ($--_{\text{Lamphun}}$) deletion based on the geographic origin of the first case.⁷ This deletion is larger than α^0 -thalassemia $--_{\text{SEA}}$ (19.3 kb) but smaller than the $--_{\text{THAI}}$ (33.4 kb) and $--_{\text{CR}}$ (44.6 kb) deletions, which are the most prevalent *cis* deletions found in the Thai population.⁸ In the present study, we reported HbH disease resulting from compound heterozygosity for $--_{\text{Lamphun}}/-\alpha^{3.7}$ in a 61-year-old Thai woman. Although this elderly case and the previous case are from unrelated families, they live in Lamphun

Province, a province in northern Thailand. Therefore, both may share the same ancestry. These two cases exhibited moderate anemia with a total Hb level of 91 gm/L; neither required blood transfusion. However, the increased serum ferritin in the subject could be explained by the pathophysiology of increased iron absorption from the gastrointestinal (GI) tract. The clinical and hematological features of the compound heterozygosity for $--_{\text{Lamphun}}/-\alpha^{3.7}$ are comparable to those of deletional HbH diseases caused by compound heterozygosity for $--_{\text{SEA}}/-\alpha^{3.7}$, $--_{\text{THAI}}/-\alpha^{3.7}$, and $--_{\text{CR}}/-\alpha^{3.7}$, and they are less severe than non-deletional HbH diseases.⁹⁻¹¹ Compound heterozygosity for α^0 -thalassemia $--_{\text{Lamphun}}$ deletion and other Hb variants, including HbCS, Hb Paksé (*HBA2*: c.429A>T), Hb Pak Num Po (*HBA1*: c.396_397insT), and Hb Quong Sze (*HBA2*: c.377T>C), may result in severe non-deletional HbH disease. Therefore, a better understanding of these cases' clinical and hematological features, especially for the new and rare α^0 -thalassemia mutation, such as the $--_{\text{Lamphun}}$ deletion and its combinations, is beneficial for management planning, genetic counseling, treatment, and family education.

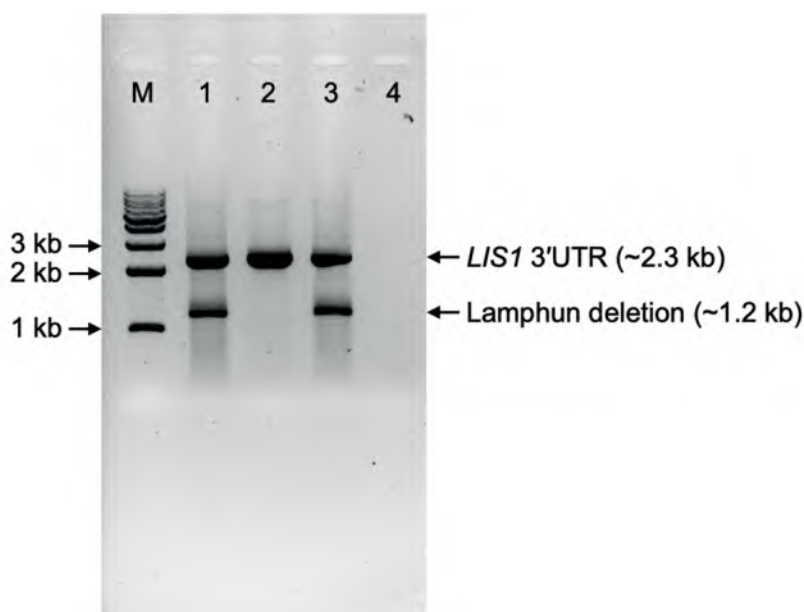


Figure 2. Conventional gap-PCR identified the α^0 -thalassemia $--_{\text{Lamphun}}$ deletion (~1.2 kb). The amplified fragments were separated by 1.0% agarose gel electrophoresis. M: 1 kb ladder DNA marker, Lanes 1, 2, 3, 4: the analysis results for the positive control, negative control, case, and no DNA template control, respectively. The amplification of the *LIS1* 3'UTR fragment (~2.3 kb) was used as an internal control.

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Ethical approval

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Conflict of interest

The authors report no conflicts of interest. They are alone responsible for the content and writing of the paper.

References

- [1] Farashi S, Harteveld CL. Molecular basis of alpha-thalassemia. *Blood Cells Mol Dis*. 2018; 70: 43-53. doi: 10.1016/j.bcmd.2017.09.004.
- [2] Harteveld CL, Higgs DR. Alpha-thalassaemia. *Orphanet J Rare Dis*. 2010; 5: 13. doi: 10.1186/1750-1172-5-13.
- [3] Laosombat V, Viprakasit V, Chotsampancharoen T, Wongchanchailert M, Khodchawan S, Chinchang W, et al. Clinical features and molecular analysis in

- Thai patients with HbH disease. *Ann Hematol.* 2009; 88(12): 1185-92. doi: 10.1007/s00277-009-0743-5.
- [4] Motiani A, Zubair M, Sonagra AD. Laboratory Evaluation of Alpha Thalassemia. StatPearls. Treasure Island (FL) ineligible companies. 2024.
- [5] Ruengdit C, Panyasai S, Kunyanone N, Phornsiri-charoenphant W, Ngamphiw C, Tongsima S, et al. Characterization and identification of Hb Bart's hydrops fetalis caused by a compound heterozygous mutation --^{SEA}/--^{CR}, a novel alpha⁰-thalassemia deletion. *Int J Lab Hematol.* 2020; 42(3): e116-e20. doi: 10.1111/ijlh.13154.
- [6] Songdej D, Kadegasem P, Sirachainan N, Ruengdit C, Punyamung M, Pornprasert S. The First Thai Case of Nondeletional HbH Disease Caused by Compound Heterozygosity for alpha-Thalassemia-1 Chiang Rai (--^{CR}) Type Deletion with Hb Constant Spring. *Hemoglobin.* 2024; 48(4): 261-4. doi: 10.1080/03630269.2024.2388661.
- [7] Khamphikham P, Tepakhan W, Tongjai S, Jan-Ngam V, Laonan A, Thimsin W, et al. Identification of a novel and rare alpha⁰-thalassemia 27.0 kb deletion with 9 bp insertion (Lamphun deletion; --^{LAMPHUN}) in a Thai family. *Int J Lab Hematol.* 2024; 46(1): 176-9. doi: 10.1111/ijlh.14177.
- [8] Ruengdit C, Punyamung M, Intasai N, Pornprasert S. Single-tube multiplex real-time PCR with EvaGreen and high-resolution melting analysis for diagnosis of alpha⁰-thalassemia--^{SEA}, --^{THAI}, and --^{CR} type deletions. *PLoS One.* 2023; 18(11): e0293838. doi: 10.1371/journal.pone.0293838.
- [9] Charoenkwan P, Taweephon R, Sae-Tung R, Thanarat-tanakorn P, Sanguansermisri T. Molecular and clinical features of Hb H disease in northern Thailand. *Hemoglobin.* 2005; 29(2): 133-40.
- [10] Pornprasert S, Salaeh NA, Tookjai M, Punyamung M, Pongpunyayuen P, Treesuwan K. Hematological Analysis in Thai Samples With Deletional and Nondeletional HbH Diseases. *Lab Med.* 2018; 49(2): 154-9. doi: 10.1093/labmed/lmx068.
- [11] Ruengdit C, Khamphikham P, Jinorose N, Pornprasert S. Hb Bart's Hydrops Fetalis Syndrome and Hb H Disease Caused by Deletional Chiang Rai (--^{CR}) alpha⁰-Thalassemia in Two Unrelated Thai Families. *Hemoglobin.* 2021; 45(2): 75-9. doi: 10.1080/03630269.2021.1906269.

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- [1] Pachori P, Gothwal R, Gandhi P. Emergence of antibiotic resistance *Pseudomonas aeruginosa* in intensive care unit; a critical review. *Genes Dis.* 2019; 6(2): 109-19. doi: 10.1016/j.gendis.2019.04.001.
- [2] Hung KN G, Fong KN. Effects of telerehabilitation in occupational therapy practice: A systematic review. *Hong Kong J Occup Ther.* 2019; 32(1): 3-21. doi: 10.1177/1569186119849119.
- [3] Wijesooriya K, Liyanage NK, Kaluarachchi M, Sawkey D. Part II: Verification of the TrueBeam head shielding model in Varian VirtualLinac via out-of-field doses. *Med Phys.* 2019; 46(2): 877-884. doi: 10.1002/mp.13263.
- [4] Velayati F, Ayatollahi H, Hemmat M. A systematic review of the effectiveness of telerehabilitation interventions for therapeutic purposes in the elderly. *Methods Inf Med.* 2020; 59(2-03): 104-9. doi: 10.1055/s-0040-1713398.
- [5] Junmee C, Siriwachirachai P, Chompoonimit A, Chanavirut R, Thaweewannakij T, Nualnetr N. Health status of patients with stroke in Ubolratana District, Khon Kaen Province: International Classification of Functioning, Disability and Health-based assessments. *Thai J Phys Ther.* 2021; 43(1): 45-63 (in Thai).

Journal Articles on the Internet

- [1] Siegel PM, Bojti I, Bassler N, Holien J, Flierl U, Wang X, et al. A DARP targeting activated Mac-1 is a novel diagnostic tool and potential anti-inflammatory agent in myocarditis, sepsis and myocardial infarction. *Basic Res Cardiol [Internet].* 2021; 116(1): 1-25. Available from: <https://doi.org/10.1007/s00395-021-00849-9>.

Journal Articles from an Online Database

- [1] Jackson D, Firtko A, Edenborough M. Personal resilience as a strategy for surviving and thriving in the face of workplace adversity: A literature review. *J Adv Nurs [serial online].* 2007;60(1):1-9. DOI: 10.1111/j.1365-2648.2007.04412.x.

Book / Chapter in an Edited Book References

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- [1] Grove SK, Cipher DJ. *Statistics for nursing research: A workbook for evidence-based practice.* 3rd ed. St. Louis, Missouri: Elsevier; 2019.
- [2] Haznadar M, editor. *Cancer metabolism: Methods and protocols.* New York: Humana Press; 2019. doi: 10.1007/978-1-4939-9027-6.
- [3] Perrin DH. The evaluation process in rehabilitation. In: Prentice WE, editor. *Rehabilitation techniques in sports medicine.* 2nd ed. St Louis, Mo: Mosby Year Book; 1994: 253–276.

E-book

- [1] Dehkharghani S, editor. *Stroke [e-book].* Brisbane (AU): Exon Publications; 2021 [cited 2021 Jul 31]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK572004/> doi: 10.36255/exonpublications.stroke.2021
- [2] Tran K, Mierzwinski-Urban M. Serial X-Ray radiography for the diagnosis of osteomyelitis: A review of diagnostic accuracy, clinical utility, cost-effectiveness, and guidelines [e-book]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 [cited 2021 Jul 31]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK562943/>

Dissertation/Thesis

- [1] On-Takrai J. Production of monoclonal antibody specific to recombinant gp41 of HIV-1 subtype E [Term paper]. Faculty of Associated Medical Sciences: Chiang Mai University; 2001 [in Thai].
- [2] Seale AC. The clinical and molecular epidemiology of streptococcus agalactiae in Kenya: maternal colonization and perinatal outcomes [Dissertation on the Internet]. [Oxford (England)]: University Oxford; 2015 [cited 2015 Jul 28]. Available from: <http://ora.ox.ac.uk/objects/uuid:6e7d952a-dc5b-4af0-b0bb-f2ae2184eed0>.

Conference Proceedings

- [1] Lake M, Isherwood J, Clansey. Determining initial knee joint loading during a single limb drop landing: reducing soft tissue errors. *Proceedings of 34th International Conference of Biomechanics in Sport*; 2016 Jul 18-22; Tsukuba, Japan, 2016. Available from: <https://ojs.ub.uni-konstanz.de/cpa/article/view/7126>
- [2] Ellis MD, Carmona C, Drogos J, Traxel S, Dewald JP. Progressive abduction loading therapy targeting flexion synergy to regain reaching function in chronic stroke: preliminary results from an RCT. *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*; 2016: 5837-40. doi: 10.1109/EMBC.2016.7592055.

Organization as Author / Government Document

- [1] Australian Government, Department of Health. *Physical activity and exercise guidelines for all Australian.* 2021 [updated 2021 May 7; cited 2021 Jul 15]. Available from: <https://www.health.gov.au/health-topics/physical-activity-and-exercise/physical-activity-and-exercise-guidelines-for-all-australians>.
- [2] Department of Health. *Situation survey on policy and implementation of physical activity promotion in schools for first year 2005.* Nonthaburi: Ministry of Public Health; 2005. (in Thai).
- [3] Department of Local Administration, Ministry of Interior Affairs. *Standard of Sports Promotion.* Bangkok. 2015: 7–9. (in Thai).
- [4] World Health Organization. *WHO guidelines on physical activity and sedentary behaviour.* Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
- [5] World Health Organization. *The epidemiology and impact of dementia: current state and future trends.* 2015 [cited 2021 Mar 8]. Available from: http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf.

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