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Correlation of Month of Birth and Socioeconomic Status with Autism Spectrum Disorder: a Nationwide Study

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Abstract

The aim of this study was to investigate whether autism spectrum disorder (ASD) is associated with birth month in Taiwan, as has been found in other countries. A case–control study (1:4) matching cases with controls according to sex and age was conducted. Based on the National Health Insurance Research Database (NHIRD) from 1996 through 2008, the study population comprised 4.3% of the population of Taiwan. Multiple logistic regression was performed after adjusting for the socioeconomic factors of urbanization level and income level. A total of 965 people with ASD and 3,860 controls were recruited. In comparison with a March birth, a higher risk of ASD was found for June and August births. After adjusting for the levels of urbanization and income, the risk of developing ASD was still higher for June, July, and August births over the year. There was a higher risk of ASD in urban areas as compared with rural areas. A higher risk of ASD was found in subjects with the highest income level, among children born in the summer months, those in urban areas, and subjects of high socioeconomic status, which suggested the presence of social-environmental causes of ASD.

Keywords: Autism spectrum disorder, Month of birth, Nationwide, Socioeconomic status, Urbanization.

Introduction

The etiology of autism spectrum disorder (ASD) is of interest in terms of considering the interactions of genes and environmental factors. Environmental risk factors influence and contribute to neural development and the formation of altered functioning in those with genetic vulnerability. Previous studies have focused on the season of conception, maternal status during pregnancy, prenatal and perinatal exposure to infections, toxins, pollutants and chemicals, and psychosocial factors, including socioeconomic status (SES).

Deviant patterns of seasonal variation in ASD births have been identified, which may point to environmental etiological factors (Lee et al., 2008). Early previous studies indicated associations between birth in winter, or in March and/or August (Barak, Ring, Sulkes, Gabbay, & Elizur, 1995) or spring and a higher risk of ASD. In order to progress epidemiological research methods in a contemporary fashion, the issue of month of birth has been explored again in a new statistical manner. Temporal clustering of autism conceptions was identified in some studies, which supported the theory that etiological agents could contribute to the observed clusters (Mazumdar, Liu, Susser, & Bearman, 2012). However, other studies did not find an association between month or season of birth and autism (Bolton, Pickles, Harrington, Macdonald, & Rutter, 1992; Kolevzon et al., 2006). This may have been due to relatively small sample sizes, the existence of other interactive or mediating variables, or methodological differences among studies that make it difficult to compare the results (Zerbo, Iosif, Delwiche, Walker, & Hertz-Picciotto, 2011). In particular, the use of months or seasons as arbitrary units of time may affect study conclusions. These inconsistencies in results may indicate that other influencing factors exist. The impact of SES on the development of ASD has also been explored. A higher prevalence of ASD in disadvantaged families has been reported in several European studies (Delobel-Ayoub et al., 2012); in the USA, however, the phenomenon is not as consistent, the prevalence of diagnosis of ASD being reported to be particularly increased in populations of high SES (Boyle et al., 2011), while under-diagnosis exists in low SES populations (Emerson, 2012). These results might indicate not the existence of a protective effect of a low SES, but rather under-identification of ASD in these populations (Thomas et al., 2012). This phenomenon has begun to diminish gradually in recent years (King & Bearman, 2011) due to an increased availability of accessible services for disadvantaged families. As SES appears to be related to both the development of ASD and medical resources accessibility, with contradictory effects, the association of SES with ASD requires multiple-factors-adjusted analysis. It is important to control environmental factors to avoid over-inference. In Asia, research of this kind is lacking, with the exception of Japan. The aim of this study was to investigate whether birth in certain months, urbanization level, and SES are related to the prevalence of ASD in Taiwan using the National Health Insurance Research Database (NHIRD) with a large sample size.

Objectives

Our objective was to investigate the relationship of factors including the birth months of ASD patients, level of urbanization, and economic incomes, with ASD. We hypothesized that birth in specific months, level of urbanization, and SES are associated with an increased risk of ASD.

Methods

Study design

This study was based on data obtained from the National Health Insurance Research Database (NHIRD), which were audited and released by the National Health Research Institute (NHRI). Taiwan's National Health Insurance (NHI) program was implemented in 1995, and now covers up to 99% of all 23,000,000 residents of Taiwan (http://www.nhi.gov.tw/). Subjects included in the NHIRD are anonymized in order to protect individual privacy. The NHIRD has been used extensively in many epidemiological studies in Taiwan. The Taiwanese NHIRD contains comprehensive health care data, including information on all inpatient and outpatient visits, procedure codes, catastrophic illness files and various data regarding drug prescriptions of the 23.5 million insured residents. The data used to perform the analyses conducted in this study were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the NHIRD. The LHID2000 consists of all original medical claims for 1,000,000 enrollees in the Taiwan NHI program from 1996 to 2008, including historical ambulatory data and inpatient care data, and was created for and publicly released to researchers. The NHRI deems that there are no statistically significant differences in terms of age or sex between the randomly-sampled group and all beneficiaries of the NHI program. Each subject's original identification number is encrypted for the sake of privacy in the LHID2000 dataset, and all claims data were able to be linked to obtain the relevant medical data required to conduct this study.

Sample

One million subjects, 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects who had at least 1 service claim in an outpatient or inpatient clinic with a principal diagnosis of ASD (ICD-9-CM code: 299) from January 1996 to December 2008 were included as the study group. An age- and sex-matched control group (4 controls for every patient in the study cohort) was randomly identified from persons in the database after eliminating patients who had been given a diagnosis of ASD. Both the level of urbanization and enrollee category (EC) were used as SES indices. The EC 1–4 group definitions were based on prior studies, EC 1 being the highest SES and EC 4 the lowest (Chen, Liu, Su, Huang & Lin, 2007).

Statistical Analysis

Multiple logistic regression was performed, in which group (ASD and non-ASD controls) was the dependent variable and birth month was the predictor; level of urbanization and income level were covariates. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All data processing and statistical analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute, Cary, NC).

Results

In total, 965 cases of ASD were identified, and 3860 non-ASD controls were matched (1:4) according to sex, age, and index year. Most study participants were male (72%), and the mean age was approximately 19 years. The demographic characteristics of the ASD group and non-ASD controls are shown in Table 1. There were significant differences in the level of urbanization and income level between the ASD group and the non-ASD controls.

Table 2 shows the birth month distributions

Table 1: Characteristics of the ASD patients and controls.

	Controls (*n* = 3,860)		ASD (*n* = 965)		t/χ^2	*p* value
Age (years)	19.11	± 20.24	19.07	± 20.29	0.05	0.96
Male	2796	72.44%	699	72.44%	0	1.00
Socio-economic status						
Urbanization level					27.04	<0.0001
Rural	367	9.5%	67	6.9%		
Suburban	1178	30.5%	233	24.1%		
Urban	2309	59.8%	662	68.6%		
Unknown	6	0.2%	3	0.3%		
EC†					44.92	<0.0001
1	286	7.41%	130	13.47%		
2	1483	38.42%	356	36.89%		
3	1059	27.44%	207	21.45%		
4	737	19.09%	189	19.59%		
Unknown	295	7.64%	83	8.60%		

ASD, autism spectrum disorder; EC, enrollee category.
†Level 1 indicates the highest level, level 4 the lowest.

of the ASD patients and the non-ASD controls. In the ASD group, there was a trough in March and a peak in August, while in the non-ASD controls, there was a trough in June and a peak in October. The distribution across the 12 months differed significantly between the ASD patients and the non-ASD controls (χ^2= 20.82, p = 0.035).

Table 2: Birth month distribution of the ASD patients and non-ASD controls.

Birth month	Controls (*n* = 3,860)		ASD (*n* = 965)	
	n	% within group	*n*	% within group
January	353	9.1%	80	8.3%
February	271	7.0%	72	7.5%
March	315	8.2%	62	6.4%
April	282	7.3%	76	7.9%
May	279	7.2%	71	7.4%
June	249	6.5%	88	9.1%
July	260	6.7%	80	8.3%
August	351	9.1%	102	10.6%
September	368	9.5%	85	8.8%
October	388	10.1%	89	9.2%
November	379	9.8%	86	8.9%
December	365	9.5%	74	7.7%

ASD, autism spectrum disorder.

We further analyzed the association of ASD with birth month, level of urbanization, and EC. When March was selected as the reference month, and the covariates were adjusted, ASD had a stronger association with birth during the months of June (aOR = 1.79; 95% CI: 1.24–2.60), July (aOR = 1.56; 95% CI: 1.07–2.27), and August (aOR = 1.51; 95% CI: 1.06–2.15. When rural residence was chosen as the reference, ASD was associated with urban areas (aOR = 1.46; 95% CI: 1.10–1.94). A higher risk of ASD was found in the EC 1 group as compared with the EC 2 (aOR = 0.54; 95% CI: 0.42–0.68), EC 3 (aOR = 0.46; 95% CI: 0.36–0.60) and EC 4 groups (aOR = 0.58; 95% CI: 0.44–0.75). These results are presented in Table 3.

Table 3: Adjusted odds ratios of multiple conditional logistic regression for ASD.

Factor	Adjusted OR	95% CI
Birth month		
January	1.15	(0.79–1.66)
February	1.30	(0.89–1.90)
March	1.00	(reference)
April	1.33	(0.91–1.94)
May	1.28	(0.88–1.88)
June	1.79	(1.24–2.60)
July	1.56	(1.07–2.27)
August	1.51	(1.06–2.15)
September	1.16	(0.80–1.68)
October	1.18	(0.82–1.70)
November	1.15	(0.80–1.65)
December	1.01	(0.70–1.47)
Socio-economic status		
Urbanization level		
Rural	1.00	(reference)
Suburban	1.05	(0.77–1.42)
Urban	1.46	(1.10–1.94)
Unknown	2.38	(0.56–10.03)
EC type[†]		
Level 1	1.00	(reference)
Level 2	0.54	(0.42–0.68)
Level 3	0.46	(0.36–0.60)
Level 4	0.58	(0.44–0.75)
Unknown	0.59	(0.43–0.82)

ASD, autism spectrum disorder; OR, odds ratio; CI, confidence interval; EC, enrollee category.
[†]Level 1 indicates the highest level, level 4 the lowest.

Discussion

In the present study, the association between month of birth and ASD was explored. We determined a significantly higher incidence of ASD in those born in June, July, and August. Our results showed that there exists an association between summer births and a higher risk of ASD, the pattern showing one peak over the 12 months. This result is consistent with previous studies indicating that there might exist two or three months in which the risk of ASD is higher. For example, results have indicated a higher risk of ASD in those born in March and August (or in winter) in the USA (Stevens, Fein, & Waterhouse, 2000); March and August in Israel (Barak et al., 1995); and March, May and June in Japan and the UK. Leezand colleagues enrolled 1068 ASD patients from USA population data, and found similar peaks in the occurrence of ASD for multiple births, but the peaks occurred 2–4 weeks earlier than for single births, in April, June/July and October (Lee et al., 2008). They posited that there are non-heritable factors in operation during the pre- or perinatal period. Maternal pregnancy status and insult to the fetus during critical periods of neurodevelopment have been discussed (Estes, & McAllister, 2015; Mackay, et al., 2016). The immune hypothesis and neuroinflammation theory (Tonhajzerova et al., 2015) in terms of the development of ASD have been addressed, and immunological evidence points to a relationship between ASD and the immune system (Gesundheit et al., 2013). Animal and human studies have shown similar trends; for example, pregnant mice with human influenza virus infection yielded adult offspring with a profound behavioral effect similar to autism (Shi, Fatemi, Sidwell, & Patterson, 2003). Maternal exposure to respiratory infections through pregnancy (Lin, Huang, Ning, & Tsao, 2004), and asthma in early life that might be a result of ambient air pollution, increase the risk of ASD. According to our results, conception of ASD patients was more common during autumn and winter, as June, July and August births were associated with a higher incidence of ASD; these are seasons with a high prevalence of several respiratory viral infections, for example, the influenza virus, adenovirus, respiratory syncytial virus, bacterial infection, etc. Whether the clustering of these conception months in Taiwan is related to maternal infection requires further clarification. In addition to maternal infection, the relationship between maternal nutrition status and ASD development has been discussed previously. Vitamin D deficiency was identified as being related to ASD in recent studies. In an animal model, mid-gestational vitamin D deficiency was found to be associated with the risk of ASD (Vinkhuyzen et al., 2017). In a large cohort study, vitamin D deficiency was identified as being related to ASD traits (Vinkhuyzen et al., 2016). The first trimester is suspected to be the period of greatest risk (Chen, Xin, Wei, Zhang, & Xiao, 2016). As the maternal vitamin D level is associated with the amount of ultra-violet exposure, the level could possibly be related to the conception month; i.e., for conceptions during autumn and winter, there will be a lower maternal ultra-violet exposure, a lower maternal vitamin D level, and a higher risk of ASD in offspring. It is worth gathering information on maternal health status during pregnancy, especially in terms of infection history and vitamin D level for the ASD cases in our study, in order to clarify the correlation and possible causal relationship.

Other environmental factors, such as exposure to toxins including chemical pollutants (Fujiwara, Morisaki, Honda, Sampei, & Tani, 2016; Landrigan, Lambertini, & Birnbaum, 2012; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013) or air pollution (Volk et al., 2013) during pregnancy have been reported to be associated with the occurrence of ASD. We attempted to explore the influence of pollution on the clustering of summer births. In Taiwan, important sources of pollution are urban areas, local industrial centers, and also nearby Asian Factors such as the weather and topography influence the accumulation and distribution of pollution. Autumn and winter are seasons in which air pollution is worsened, as the northeast monsoon occurs during that period, and the location of the central mountains leads to an accumulation of pollution, especially in mid-southern Taiwan (http://www.taqm.epa.gov.tw). A previous study in Taiwan proved that multiple common pollutants including PM10, CO, SO2, NO2, O3, and hydrocarbons influence neurobehavioral development up to 18 months of age (Lin, et al., 2014). Another study reported an influence of the presence of an incinerator on child development (Lung, Chiang, Lin, & Shu, 2013). A preliminary cohort study also indicated that prenatal exposure to CO and NO2, the levels of which are higher in winter, followed by autumn, spring, and summer, increased the risk of developing ASD, with hazard ratios ranging from 1.18 to 1.93 (Wang, personal communication). Whether or not our results indicating a higher risk of ASD in conception months during autumn and winter suggested a correlation of ASD development with maternal exposure to air pollution, more detailed demographic data and analyses are necessary for study focusing on ASD development in populations of specific areas, for example, industrial towns, areas of close proximity to major sources of pollution, and regions with higher levels of air pollution. The association of SES with ASD also varies according to our results. A higher SES and urban areas had stronger associations with ASD, similar to the phenomena observed in the USA previously. According to previous Taiwanese studies, persons with ASD living in suburban and rural areas tend to receive a diagnosis at an older age, and the duration of the diagnostic process is greater (Chen, Liu, Su, Huang, & Lin, 2008); in addition, an elevated incidence rate of ASD was found in later birth cohorts (Chen, Liu, Su, Huang, & Lin, 2007). The higher prevalences of ASD in families of higher SES and a higher level of urbanization observed in Taiwan were consistent with these study results, and might suggest better awareness of signs of ASD and good accessibility of resources in privileged families. It is not known whether heterogeneity of ASD subtypes exists between high and low SES populations, and whether ASD characteristics are truly more common as a trait among high SES populations requires further study. Use of medical resources for the screening and treatment of ASD in low SES populations is also worthy of study in order to provide a reference for the modification of public health policy regarding ASD intervention.

Limitations

There were some limitations of this study. First of all, although we used the National Health Insurance Database, the sample size was not large enough to allow further analysis of the interaction between each environmental factor and its contribution to and relationship with the process of ASD development. Secondly, the trimester, not the season of birth, may play a more important role in the risk of ASD; however, the data were anonymized, and did not provide consanguinity for every individual. Thirdly, the ASD group was heterogeneous in terms of severity; different ASD subtypes, such as subjects with differing cognitive function and symptom severity, and their associations with environmental factors and SES, should be investigated further. Finally, the number of cases of autism identified in this study was relatively small in comparison with the previously reported ratio of 1:68 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators & Centers for Disease Control and Prevention (CDC) 2014). This may indicate that the individuals with ASD in this study had a high symptom severity. This group lacks sample representation, meaning that we should be wary and cautious when considering the season of birth of high-functioning ASD patients.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest in relation to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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