

Strategies for multivariable analysis in exploratory research: an example of risk factors for chronic kidney disease

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Abstract

Researchers often want to identify and explore the relationships between multiple risk factors and an outcome of interests. This kind of research requires multiple regression analysis, due to the multiple risk factors of interests. Stepwise regression is a strategy commonly used in selecting multiple risk factors in a multivariable analysis. Unfortunately, it can lead to inadequate use of information and sometimes offers little in terms of the implications of interventions. In reality, different analysis strategies, using various plausible frameworks, are required for such research. Researchers need to consider the effects of potential confounders and the relationships between risk factors themselves in the multivariable analysis. This can help to disentangle the mechanisms by which these risk factors associate with the outcome of interests, and provide interpretable and meaningful results that help to inform for an evidence-based policy and interventions. **Chiang Mai Medical Journal 2013;52(1-2):23-31.**

Keywords: multivariable analysis, stepwise regression, risk factors and chronic kidney disease

Introduction

Researchers often want to identify and explore the relationships between multiple risk factors and a particular outcome (or disease) of interests. This type of study is called explanatory research. It is formally defined as “A study...whose main objective is to explain... a situation by isolating effects of specific variables (risk factors) and understand the mechanisms of action”[1], and it requires two key steps. The first step estimates the crude association of each specific risk factor with the outcome. The second one understands

the mechanisms of actions. Understanding of the mechanism requires inter-relationship 1) between the multiple risk factors themselves and 2) between the multiple risk factors and an outcome. When there are many risk factors to consider, a key analytical decision must be made on how to consider them together with respect to the outcome of interests. A common strategy found in much medical literature of this sort is use of the stepwise approach [2-4], which is based purely on strength of statistical association; the p-value [5]. For outcomes from which

risk factors are already known, the stepwise approach can lead to misleading conclusions and could offer little in terms of public health impact [6].

This paper considered the rationale for different strategies in multivariable analysis for exploratory research. The first strategy formed the framework for isolating the crude association of each risk factor with the outcome. Subsequent strategies for the analysis concerned four different frameworks, which accounted for the inter-relationship between risk factors, by carefully considering those that were potential confounders, and the temporal relationship in how these risk factors could be related. This paper also examined the interpretation and implications of the results under different strategies for multivariable analysis. Finally, it compared different strategies to the stepwise approach in order to highlight limitations of the latter in exploratory research.

This paper presents data from the Maharaj Nakorn Chiang Mai Health Personnel Survey, which was conducted in 2008. Identification and explanation of the risk factors associated with chronic kidney disease (CKD) in the study population was a later objective of the survey (Research ID 991/Study code FAM-12-991-EX, funded by the Faculty of Medicine, Chiang Mai University). For simplicity, this paper restricted the number of interesting risk factors to nine: age, gender, current smoking, current alcohol consumption, body mass index (BMI), systolic blood pressure (SBP), fasting blood glucose, total cholesterol (TC) and uric acid level.

The dataset and variable definition

A health survey of personnel at Chiang Mai University (CMU) Hospital was conducted in 2008 in order to collect data on self-reported risk factors and prevalence of common diseases such as hypertension and diabetes [7]. Additional laboratory investigations were offered to those at high risk of developing chronic diseases. The dataset of this paper consisted of 2,483 participants,

with complete medical records for diagnosing CKD, in accordance with National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines [8]. Estimations of glomerular infiltration rates were calculated using the modified Jaffe method [9]. CKD staging was as follows: stage I and II were defined as GFR >90 and 60–89 mL/min/1.73 m², respectively, with a hematuria and/or an albumin–creatinine ratio of 30 mg/g or greater. Stage III, IV and V were defined as GFR 30–59, 15–29 and <15 mL/min/1.73 m², respectively, regardless of kidney damage.

This paper provided information on the nine risk factors mentioned above. Six of them: age, BMI, systolic blood pressure, fasting blood glucose, total cholesterol and uric acid level, were each entered as a continuous variable. Gender, current smoking, current alcohol consumption as well as the presence of CKD (any stage) were entered as binary variables. Multiple logistic regression analysis was used to identify association between the nine risk factors and CKD. All analyses were performed using STATA 12.

Characteristics of the study population

The mean age (SD) of the participants was 42.5 (8.4) years old, with females making up the majority (73%). The risk factors stratified by gender are shown in Table 1. In general, males had higher risks than females. Men smoked and drank more than females and their mean systolic blood pressure, fasting blood sugar, total cholesterol and uric acid level were higher. Characteristics of the study population by CKD status are presented in Table 2.

1. Modeling strategy for univariable analysis: To isolate the crude effect of each risk factor. The aim of this strategy was to estimate the crude association between each of the nine risk factors of interest with outcome, which is CKD. The results suggested that all risk factors, except current smoking, were associated with CKD (Table 3). Interestingly, current smoking and current alcohol consumption seem to be associated with reduce risks of CKD. The frame-

Table 1. Characteristics of the study population

Characteristics	Male (n=668)	Female (n=1,815)	Total (n=2,483)
Mean age in years (SD)	43.2 (8.2)	42.2 (8.5)	42.5 (8.4)
Number of current smokers (%)	131 (19.6)	3 (0.2)	134 (5.4)
Number of current alcohol drinkers (%)	470 (70.4)	327 (18.0)	707 (32.1)
Mean BMI in kg/m ² (SD)	24.3 (3.1)	22.4 (3.3)	23.0 (3.4)
Mean systolic blood pressure in mmHg (SD)	123.5 (13.6)	113.5 (12.0)	116.2 (13.2)
Mean fasting blood sugar level in mg/dL (SD)	95.9 (32.5)	87.4 (14.6)	89.8 (21.6)
Mean total cholesterol level in mg/dL (SD)	223.7 (47.6)	217.9 (39.2)	219.5 (41.8)
Mean uric acid level in mg/dL (SD)	6.6 (1.5)	4.2 (1.1)	4.9 (1.6)

Table 2. Characteristics of the study population with and without chronic kidney disease (CKD)

Characteristics	With CKD: any stage (n=1,029)	Without CKD (n=1,454)	<i>p</i>
Mean age in years (SD)	45.5 (7.6)	40.3 (8.3)	<0.01*
Number of females (%)	797 (77.5)	1,018 (70.0)	<0.01**
Number of current smokers (%)	45 (4.4)	89 (6.2)	0.059**
Number of current alcohol drinkers (%)	282 (27.4)	515 (35.4)	<0.01**
Mean BMI in kg/m ² (SD)	23.4 (3.4)	22.6 (3.3)	<0.01*
Mean systolic blood pressure in mmHg (SD)	117.5 (13.6)	115.3 (12.9)	<0.01*
Mean fasting blood sugar level in mg/dL (SD)	91.6 (24.0)	88.4 (19.4)	<0.01*
Mean total cholesterol level in mg/dL (SD)	224.6 (44.4)	215.5 (39.1)	<0.01*
Mean uric acid level in mg/dL (SD)	5.0 (1.6)	4.8 (1.6)	<0.01*

*p-value from t-tests, **p-value from chi-square tests

work (Figure 1A) in this analysis does not consider the relationship between the risk factors themselves, and cannot offer any explanation for the underlying mechanisms of the association seen, which is therefore prone to bias, due to confounding caused by the relationships between the risk factors themselves and the outcome. The issue of confounding was explored in the next strategy.

2. Modeling strategy to consider the inter-relationship between risk factors

2.1 Adjusting for known confounders (age and gender) Confounding is defined as “the distortion of a measure of the effect of an exposure on an outcome due to the association of

the exposure of other factors that influence the occurrence of the outcome” [1]. For example, if age is associated with increased risk factors (such as BMI and systolic blood pressure), and is connected also to an increased risk in outcome (CKD), the association found in the univariable analysis between the risk factors (such as BMI and systolic blood pressure) and CKD is biased, due to distortion influenced by age. This case is plausible and the dataset indeed provides evidence that 1) age and sex are associated independently with the remaining seven risk factors of interests, and 2) age and sex are associated independently also with CKD. This fits the definition of confounders as previously defined.

This second strategy is now a multivariable model and considers age and gender as confounders in the association between the seven remaining risk factors and CKD (Figure 1B). The adjusted associations seen in people of the same age and gender are interpreted as the connection between the risk factors and CKD. A comparison between the crude and adjusted association between the risk factors of interests and CDK are shown in Table 3. The associations between current smoking and current alcohol drinking with CKD (adjusted for age and gender) have increased. An explanation of the changes in associations can be offered by carefully considering the information provided in Tables 1, 2 and 3. Firstly, Table 1 shows that being female is associated negatively with smoking (i.e. females are associated with less smoking when compared to males). Secondly, being female is associated strongly with an increased risk of CKD, with an Odds Ratio (OR) of 1.47 (95% CI 1.22 to 1.77). The fact that smokers are less likely to be female, and females are more likely to have CKD, explains why current smoking was associated with decreased risks of CKD in the univariable analysis (Table 3 column A). After adjusting for age and gender, the association between current smoking and CKD increased from an OR of 0.7 in the crude analysis to that of 1.08 in the adjusted analysis (Table 2 column B). The same direction of confounding applies to the relationship between current alcohol consumption and CKD.

Results in the adjusted analysis (Table 2 column B) can summarize that BMI, systolic blood pressure, fasting blood glucose, total cholesterol and uric acid level in people of the same age and gender are all associated significantly with CKD. This result is consistent with previous findings in the literature [10, 11].

2.2 Considering the inter-relationship between risk factors using a hierarchical framework

Victoria et al (1997) described strategies in detail for handling complex inter-relationships between risk factors [12]. For example, in this study, current smoking, current alcohol con-

Table 3. Comparison between crude and adjusted odds ratio (OR) of risk factors for chronic kidney disease (CKD)

Risk factors	Column A Unadjusted OR (95% CI)	Column B Age-gender adjusted OR (95% CI)
1. Age (increase)	1.08 (1.07 to 1.10) <0.01	---
2. Gender (female)	1.47 (1.22 to 1.77) <0.01	---
3. Current smoking	0.70 (0.48 to 1.01) $p=0.059$	1.08 (0.71 to 1.64) $p=0.72$
4. Current alcohol drinking	0.69 (0.58 to 0.82) $p<0.01$	0.93 (0.75 to 1.14) $p=0.49$
5. BMI (increase)	1.07 (1.05 to 1.10) $p<0.01$	1.06 (1.02 to 1.08) $p<0.01$
6. SBP (increase)	1.01 (1.01 to 1.02) $p<0.01$	1.01 (1.00 to 1.02) $p<0.01$
7. FBS (increase)	1.00 (1.00 to 1.01) $p<0.01$	1.00 (1.00 to 1.01) $p<0.01$
8. TC (increase)	1.00 (1.00 to 1.01) $p<0.01$	1.00 (1.00 to 1.01) $p<0.01$
9. Uric acid (increase)	1.10 (1.04 to 1.16) $p<0.01$	1.40 (1.30 to 1.52) $p<0.01$

sumption and BMI could be grouped as behavioral risk factors because they can be treated mainly with lifestyle modification. The remaining risk factors; systolic blood pressure, fasting blood glucose, total cholesterol and uric acid level can be grouped as physiological risk factors, all of which can be treated mainly with pharmacological treatment. Figure 1C depicts the framework, where the effects of behavioral risk factors on

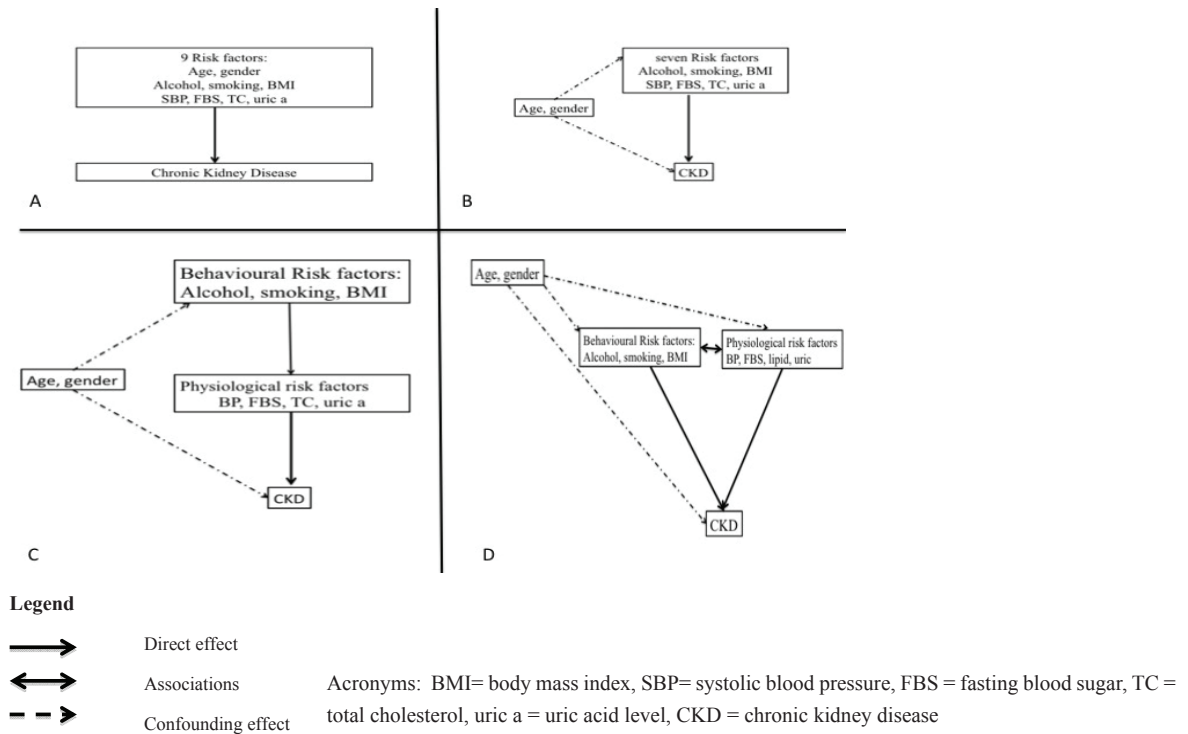


Figure 1. Different Framework for analysis of the relationship between nine risk factors and Chronic Kidney Disease:

A, Framework for estimating the effect of each specific risk factor; **B**, Framework for estimating the effect of each risk factor adjusted for confounders (age and gender); **C**, Hierarchical framework for estimating the effect of behavioral risk factors adjusted for confounders (age and gender); **D**, Non-hierarchical framework for estimating the effect of behavioral and physiological risk factors adjusted for confounders (age and gender)

CKD are mediated entirely through physiological risk factors. This strategy for analysis could not adjust for the physiological risk factors when exploring the association between behavioral risk factors and CKD, as they are on the causal pathway [13]. Instead, this analysis would start with a multivariable model, where all three behavioral risk factors are included together. As age and gender are confounders, they are always included in the multivariable model. The behavioral risk factors are then removed one by one, starting from the least significant, and kept in the model only if remaining statistically significant ($p < 0.05$). Results of the different models that used this strategy are shown in Table 4. Due to the confounding effect of age and gender on current smoking and current alcohol consumption, it is not surprising that of the three behavioral

risk factors; only BMI remained independently significant after adjusting for age and gender.

Finding BMI as an independent behavioral risk factor for CKD has been proved in only part of the framework proposed in Figure 1C. To provide evidence that supports Figure 1C, proof is needed that BMI is associated also with physiological risk factors such as blood pressure, fasting blood glucose, total cholesterol and uric acid level. In using linear regression, the dataset provides evidence that increased BMI is associated with an increase in all four physiological risk factors in people of the same age and gender (Table 5).

The summary of this framework needs to combine evidence from Tables 3, 4 and 5, which can interpret that one unit increase in BMI is associated with a 6% increase in the odds of CKD

Table 4. Multivariable model considering all behavioral risk factors adjusted for age and gender

Behavioral risk factors	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1. Current smoking	1.11 (0.73 to 1.68)	0.63	---	--	--	--
2. Current alcohol consumption	0.92 (0.74 to 1.09)	0.41	0.92 (0.74 to 1.14)	0.44	--	--
3. BMI	1.06 (1.03 to 1.09)	<0.01	1.06 (1.03 to 1.09)	<0.01	1.06 (1.03 to 1.09)	<0.01

Model 1 explanatory variables included in the logistic regression models: age, gender, current smoking, current alcohol consumption and body mass index (BMI)

Model 2 explanatory variables included in the logistic regression models: age, gender, current alcohol consumption and body mass index (BMI)

Model 3 explanatory variables included in the logistic regression models: age, gender and body mass index (BMI)

Table 5. Association between BMI and controlled physiological risk factors using linear regression for age and gender

Physiological risk factors	β for BMI*	95% CI	<i>p</i>
1. Systolic blood pressure	1.08	0.93 to 1.22	<0.01
2. Fasting blood sugar	0.95	0.68 to 1.21	<0.01
3. Total cholesterol	0.67	0.12 to 1.24	0.02
4. Uric acid level	0.10	0.08 to 0.12	<0.01

* all models adjusted for age and gender by using linear regression

in people of the same age and gender. This association between BMI and CKD is mediated possibly by the physiological risk factors. Data showed that increased BMI is associated also with increased risks in all four physiological risk factors (Table 5), all of which are associated with increased risk of CKD (Table 3 column B).

2.3 Considering the inter-relationship between risk factors using a non-hierarchical framework

The framework in Figure 1C assumes that the effect of behavioral risk factors is mediated entirely by physiological risk factors. This may not be entirely true, as BMI in people with the same physiological risk factors could still have an independent effect on CKD. This non-

hierarchical framework is now depicted in Figure 1D. In this framework, the modeling strategy would need to combine the behavioral and physiological risk factors together. One strategy is to model only the behavioral and physiological risk factors separately before combining only the variables that remain significant from each group together. Modeling only the behavioral risk factors results in the same model as that presented in Table 4. Modeling only the physiological risk factors together needs careful consideration regarding their relationship, as all of them correlate positively with each other ($p < 0.01$ in all pairwise correlations). In selecting these variables together, a strategy similar to the step-wise approach could be used by modeling all

four physiological risk factors together (with age and gender as explanatory variables). The physiological risk factors would be removed one by one by starting from the least significant, until all of the remaining ones are statistically significant. From this approach, the remaining physiological risk factors would be total cholesterol and uric acid (Table 6: Model 1).

However, since there is evidence that all these risk factors correlate positively with each other, this stepwise approach is arguable. It could be considered whether or not and how the physiological risk factors excluded from the stepwise approach (systolic blood pressure and fasting blood sugar) are associated with CKD. This argument is based on biological plausibility and potential for future implications because systolic blood pressure and fasting blood sugar are measured more commonly. Model 2 (in Table 6) shows some evidence that both higher levels of systolic blood pressure and fasting blood sugar are associated with higher risks of CKD among people of the same age and gender.

No results in Model 1 or 2 from Table 6 can be considered as incorrect, and there is no clear answer that says which model is better than the other. It would be best to keep and explore both models further. By adding the one remaining significant behavioral risk factors (BMI) to Model 1 in Table 6, the BMI became insignificant. In contrast, When the BMI was added to Model 2 in Table 6, both systolic blood pressure and fasting blood pressure lost significance.

As a result, the researchers working in this non-hierarchical framework would have to think carefully about the results in both Model 1 and 2 from Table 5, as the two models have different interpretations and implications for interventions. When adjusting for age and gender, the results from Model 1 (in Table 6) present data that states uric acid level is the strongest risk factor for CKD. This raises the importance of being aware and in control of such risk factors. The results from Model 2 (in Table 6) raise the importance of commonly measured physiological risk factors; systolic blood pressure and fasting blood

Table 6. Multivariable model considering physiological risk factors adjusted for age and gender

Physiological risk factors	Model 1 OR (95% CI)	Model 2 OR (95% CI)
1. Systolic blood pressure	--	1.01 (1.00 to 1.02) <i>p</i> 0.01
2. Fasting blood sugar	--	1.00 (1.00 to 1.01) <i>p</i> 0.06
3. Total cholesterol	1.00 (1.00 to 1.01) <i>p</i> <0.01	--
4. Uric acid level	1.39 (1.28 to 1.50) <i>p</i> <0.01	--

Model 1 explanatory variables included in the logistic regression models: age, gender, total cholesterol and uric acid

Model 2 explanatory variables included in the logistic regression models: age, gender, systolic blood pressure and fasting blood sugar

sugar. By Model 2 losing its significant level as an explanatory variable after adding BMI, it also provides information that blood pressure and fasting blood glucose can be modulated by controlled BMI. Both these points are important and can result in different public health interventions. In reality, there is no need to present only one “final” model. Every model presented so far provides some useful information about the mechanisms by which these risk factors are associated with CKD. All of these risk factors can lead to an evidence-based policy and intervention for the prevention of CKD.

Comparison of results with the stepwise approach

The stepwise approach would have considered all nine risk factors together because all of them were associated significantly with CKD (Table 2). This would be carried out without con-

sidering which factors could be seen as confounders, and the relationship between the risk factors themselves would be disregarded completely. By using this approach, the result would suggest that only age, gender, uric acid and cholesterol are associated independently with CKD, and the other risk factors would have been disregarded completely. It would be impossible to disentangle the mechanisms by which these risk factors are associated with CKD without going through the steps described above, and thus, only limited implications of the findings can be provided.

Conclusion

This paper shows that in an exploratory research, stepwise regression leads to inadequate use of information and offers little in terms of implications for interventions. Careful consideration using a different plausible framework for analysis can help to disentangle the mechanisms, by which these risk factors are associated with the outcome of interest. This stresses the importance of a clear framework based on biological plausibility and temporal relationships between risk factors. In terms of choosing different models, there is no need for one “final” model for such exploratory research questions. The interpretation and public health implication of the findings need to be considered. As George E. Box, a famous statistician wrote, “essentially, all models are wrong, but some are useful.”

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แผนการวิเคราะห์งานวิจัยเพื่อค้นหาความเสี่ยงและกลไกการเกิดโรคที่มีหลายตัวแปร: ตัวอย่างจากปัจจัยเสี่ยงของ โรคไตวายเรื้อรัง

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ภาควิชาเวชศาสตร์ครอบครัว คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บ่อยครั้งที่นักวิจัยต้องการศึกษาเพื่อค้นหาความสัมพันธ์และศึกษากลไกระหว่างปัจจัยเสี่ยงหลายชนิดกับโรคใดโรคหนึ่ง ซึ่งจำเป็นต้องใช้การวิเคราะห์ที่เรียกว่า การวิเคราะห์การถดถอยพหุคูณ (multiple regression analysis) แนวทางการเลือกปัจจัยเสี่ยงหรือตัวแปรที่พบบ่อยในการวิจัยลักษณะนี้คือ การวิเคราะห์แบบขั้นบันได (stepwise regression) อย่างไรก็ตามการเลือกตัวแปรแบบขั้นบันได ไม่สามารถใช้ประโยชน์จากข้อมูลที่ได้ทำการเก็บมาอย่างเต็มที่ และข้อสรุปที่ได้อาจมีข้อจำกัดในการนำไปใช้ประโยชน์เพื่อกำหนดนโยบายในการป้องกันโรค ในความเป็นจริงการวิเคราะห์ลักษณะงานวิจัยแบบดังกล่าว จำเป็นต้องอาศัยกรอบความคิด (framework) ของกลไกการเกิดโรคหลายกรอบ เพื่อเลือกปัจจัยเสี่ยงหรือตัวแปรต่างๆ กรอบความคิดดังกล่าวต้องคำนึงถึงปัจจัยกวน (confounder) และความสัมพันธ์ระหว่างปัจจัยเสี่ยงต่าง ๆ ที่มีต่อกันและกัน ซึ่งการวิเคราะห์แบบดังกล่าวจะช่วยให้เข้าใจกลไก และความสัมพันธ์ระหว่างปัจจัยเสี่ยงต่อการเกิดโรค เพื่อข้อสรุปที่เกิดขึ้นจะสามารถนำมาทำประโยชน์ในการกำหนดนโยบายเพื่อป้องกันโรคและดูแลรักษาโรคได้ *เชียงใหม่เวชสาร* 2556;52(1-2)23-31.

คำสำคัญ: การวิเคราะห์การถดถอยพหุคูณ การวิเคราะห์แบบขั้นบันได ปัจจัยเสี่ยง โรคไตเรื้อรัง