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COMMENTARY

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Commentary on "Determinants of pre-eclampsia among pregnant women attending perinatal care in hospitals of the Omo district, Southern Ethiopia"

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In the issue of *The Journal of Clinical Hypertension*, the article entitled "Determinants of pre-eclampsia in pregnant women attending hospitals in the Omo district of Southern Ethiopia" by Kassahun and colleagues examined factors associated with pre-eclampsia in Southern Ethiopia.[1] They performed logistic regression analysis to identify factors, and reported that history of chronic hypertension in a primary relative, family history of diabetes mellitus, preterm gestation, and pre-conception smoking exposure are associated with an increased risk of pre-eclampsia. This study reveals important data and clinical implications for pregnant women in low- and middle-income countries, such as Ethiopia.

Pre-eclampsia is a pregnancy complication characterized by high blood pressure and signs of damage to other organ systems, and its cause remains largely unknown.[2] The leading hypotheses strongly rely on disturbed placental function in early pregnancy.[3] Globally, 10%–15% of all maternal deaths are attributable to pre-eclampsia or eclampsia.[4,5] Previous studies have reported several risk factors for pre-eclampsia, including age, body mass index, multiple pregnancy, pre-eclampsia in any previous pregnancy, pre-existing hypertension, pre-existing renal disease, pre-existing diabetes, presence of antiphospholipid antibodies, and family history of pre-eclampsia.[3] Investigating risk factors enables us to identify optimal population for pharmacotherapy. Individual patient data meta-analysis showed that aspirin administration had potential to prevent pre-eclampsia.[6,7] Thus, early prediction of pre-eclampsia leads to improving maternal and perinatal outcomes. A notable point in the article by Kassahun and colleagues is that their study focused on family history of chronic diseases, such as hypertension and diabetes mellitus, without limiting the history to the participant's mother or sister. Genetic associations of pre-eclampsia have been reported. Nilsson and colleagues[8] reported that a full sister to a woman with pre-eclampsia and daughter to a woman with pre-eclampsia had an increased risk of pre-eclampsia in Sweden. They estimated that the heritability of pre-eclampsia was 31% among 1 188 207 births and their parents.[8] Ward and Taylor suggest that the risk for pre-eclampsia is 20%–40% in daughters of pre-eclamptic mothers, and 11%–37% in sisters of pre-eclamptic women.[9] Twin studies have estimated that approximately 22%–47% of preeclampsia risk is heritable.[8,10–13] Although these studies mainly focused on daughter-mother or inter-sister associations of pre-eclampsia, the findings of Kassahun and colleagues indicate that the risk of pre-eclampsia might be related to the presence of these chronic diseases in any close relative, without limiting the association to the subject's mother or sister. This indicates that determination of the risk of preeclampsia requires detailed pedigree information, eg Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study.[14] Another notable point in Kassahun and colleagues' article is that a positive association was found between pre-conception smoking and increased risk of pre-eclampsia. This finding was opposed to results of previous studies. Bainbridge and colleagues[15] reported that women who smoke cigarettes throughout

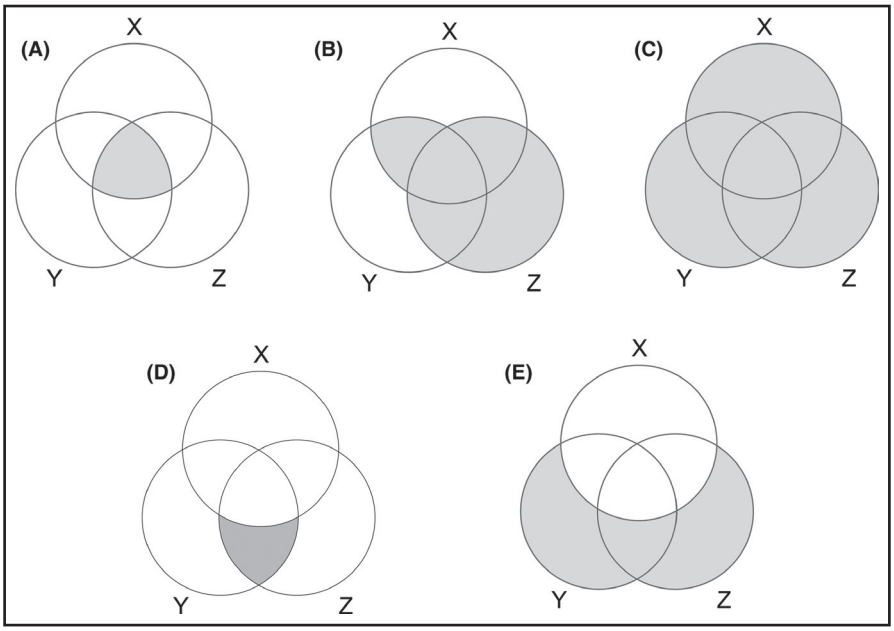

FIGURE 1 Five examples of interrelations among X, Y, and Z for explaining O using a Venn diagram. (A-E) correspond to the following interrelations: O = X "and" Y "and" Z, O = X "and" Y "or" Z, O = X "or" Y "or" Z, O = –X "and" (Y "and" Z) and O = –X "and" (Y "or" Z), respectively. In each Venn diagram, gray colored part explains outcome (O)

pregnancy are at a 33% reduced risk of developing pre-eclampsia. Some mechanisms such as soluble fms-like tyrosine kinase-1, soluble endoglin, vascular endothelial growth factor, and adrenomedullin pathway have been proposed in terms of a protective effect against the development of pre-eclampsia by smoking.[16–18] As smoking also has negative effect on pregnant woman and fetus,[19] discussion with wide perspective should be done about smoking during pregnancy.

As Kassahun and colleagues themselves mentioned, there is no single definite factor that predicts pre-eclampsia.[20,21] The risk factors for pre-eclampsia might be interrelated, and such interrelation should be investigated. However, there are limited statistical methods for estimating comprehensive risks in cases with the concurrent presence of several risk factors, making it difficult to evaluate the interrelation between patient characteristics and comorbidities in terms of outcomes. To evaluate the interrelations among characteristics and comorbidities, a method called the Boolean Monte Carlo method (BMCM) has been proposed.[22] In medicine, binary values (often represented by 0 and 1) are used to represent patient characteristics, medical test results, and the presence of disease (positive or negative). Binary values can be calculated using Boolean operators (often represented by "and" and "or"), which can be regarded as an interrelation (Figure 1). In each Venn diagram drawn in Figure 1, gray colored part can be interpreted as an interrelation which contributes the outcome. For example, in Figure 1A, a patient who has three factors (X, Y and Z) at once tends to have outcome (O). In BMCM, Boolean operators are randomly assigned between binary variables, and focus on the frequencies of operators that can accurately explain outcomes. According to these processes, the interrelations of variables for explaining outcomes can be statistically determined, and statistical parameters, such as sensitivity and specificity, can be calculated. In a previous study, interrelations among patient characteristics and symptoms and outcomes were discussed using BMCM.[23] In this previous study, the authors compared BMCM using a contingency table and logistic regression model.[23] Contingency tables or logistic regression models are often used to determine risk factors. Although these methods are useful, they have some limitations when dealing with the interrelations between patient characteristics and symptoms. These limitations arise from the assumption that explanatory variables are independent of each other. Although BMCM can be applied only to binary values, BMCM might be an additional method for determining the interrelations between variables. Performing BMCM, in addition to the analyses by Kassahun and colleagues, might help to clarify the features of pre-eclampsia. Using BMCM, interrelations among factors such as history of chronic hypertension in a primary relative, family history of diabetes mellitus, preterm gestation, and pre-conception smoking exposure can be determined in order to more accurately predict the risk of pre-eclampsia. Although pre-eclampsia remains one of the most important multifactorial diseases during pregnancy, its underlying mechanisms are still unclear. A step-by-step investigation of the pathogenesis of pre-eclampsia, including its genetic and environmental aspects, would help to unravel its complex mechanisms, and improve maternal and perinatal outcomes.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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