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CORRESPONDENCE

Association between the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to preeclampsia: the need for data clarification in a recent meta-analysis

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We recently read the paper by Xia *et al.*[1] with great interest. The authors identified a total of 34 eligible studies (36 cohorts) with 4253 patients with preeclampsia (PE) and 4950 controls and performed a meta-analysis to examine the association between the methylenetetrahydrofolate reductase (*MTHFR*) C677T polymorphism and PE susceptibility. The results indicated that the *MTHFR* C677T polymorphism is capable of increasing PE susceptibility in the Asian population but not in Caucasians. Although their study was interesting, we would like to raise several concerns related to their article.

First, Hardy–Weinberg equilibrium (*HWE*) in the control subjects should be estimated in the meta-analysis using Fisher's exact test, with $P<0.05$ considered statistically significant.[2] The authors' report indicated that four studies were excluded because the genotype distribution in the control population deviated significantly from *HWE*.[3–6] However, when we performed the calculation, we found that the first three studies did not deviate significantly from *HWE* ($P_1=0.0664$, $P_2=0.1290$, $P_3=0.0783$). In addition, the genotype information of the PE patients cannot be extracted from the study by Murphy *et al.*[6] Importantly, there is no current consensus on whether to include studies that are not in *HWE* in such analyses. However, Thakkinstian[7] suggests that sensitivity analyses should be performed with and without these studies to test the robustness of the results. Therefore, we believe that bias would be introduced into the results of the meta-analysis owing to this shortage.

Second, using the same search strategy and end-of-search date as Xia *et al.*,[1] we located 15 other relevant case–control studies[5,8–21] that were not included in the meta-analysis even though they satisfied the search criteria with a total of 1509 cases and 4080 controls. One of the 15 studies was performed in an Asian population, and 14 studies were performed in Caucasian populations. Although the available data could be obtained from these 15 studies to calculate the odds ratios with confidence intervals and the results for the recessive genetic model in particular, the authors omitted them. We believe the new participants will affect the final results of the meta-analysis of the association between the *MTHFR* gene C677T polymorphism and the risk of PE.

Third, our previous study indicated that the frequencies of the −677T *MTHFR* gene polymorphism were different between East Asian (China, Japan, and Korea) and South Asian (India) populations.[22] In an ethnicity-specific subgroup analysis, these two populations should not be pooled as one Asian population. If they are forcibly pooled, obvious heterogeneity will be detected. Coincidently, Xia *et al.*[1] determined that a study in India was the origin of the heterogeneity in the Asian population subgroup analysis. However, they did not explain the cause of the phenomenon. In addition, because only 735 PE patients and 1033 controls were involved in the Asian population subgroup analysis and significant heterogeneity was detected, further studies based on larger and more homogeneous samples are needed to assess the association between the *MTHFR* gene C677T polymorphism and susceptibility to PE in the Asian population to reach a definitive conclusion.

In conclusion, the results of the study by Xia *et al.*[1] should be interpreted with caution. We believe that our remarks will contribute to a more accurate elaboration of the results presented by Xia *et al.*[1]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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