Letter to the editor

**Harnessing the full potential of Mendelian randomization in genetic analyses**

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The recent article by Siedlinski and colleagues in *Circulation* investigated the relationship between circulating white blood cell counts and systemic blood pressure measures1. Using conventional observational and Mendelian randomization approaches, the authors concluded that an elevated lymphocyte count may play a causal role in the development of hypertension1. The work was carefully performed and offers useful advances. Given recent developments in Mendelian randomization methods, there may be additional analyses that could be performed to offer further insight.

Firstly, in their conventional observational analysis, the authors identified evidence of non-linear trends in the association between lymphocyte count and blood pressure traits. For example, there was a greater difference in blood pressure between the fifth and fourth quintiles of lymphocyte count than the second and first quintiles. In contrast, the Mendelian randomization analysis that was performed assumed that there was a linear effect of lymphocyte count on blood pressure. Methods for investigating non-linear associations of genetically predicted lymphocyte count on blood pressure with Mendelian randomization are available2, and could be incorporated.

Secondly, the authors noted that white blood cell indices correlate with each other. Their Mendelian randomization results identified effects of genetically predicted eosinophil count on diastolic blood pressure. As the genetic variants used as instruments for lymphocyte count are likely to also affect eosinophil count, it is unclear whether the observed association of genetically predicted lymphocyte count on blood pressure would persist after adjusting for genetically predicted eosinophil count. Multivariable Mendelian randomization methods to disentangle this are available3, and could be incorporated.

Thirdly, the authors concluded that the molecular mechanisms underlying the association between genetically predicted lymphocyte count and blood pressure might involve pathways related to albuminuria. This was based on an association between genetically predicted lymphocyte count and urinary albumin to creatinine ratio. Formal Mendelian randomization mediation analysis methods to investigate whether any effect of genetically predicted lymphocyte count on blood pressure traits might be occurring through albuminuria are available4, and could be incorporated.

To summarize, Mendelian randomization methods continue to grow and offer opportunity to draw additional insight towards strengthening the conclusions of genetic analyses. Where feasible and appropriate, they might be incorporated to this effect.

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