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Letters to the Editor

Genetically Predicted Antibody Levels as a Proxy for *Helicobacter pylori* Infection

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To the editor.

I read with interest paper by Chen et al. present a Mendelian randomization (MR) study investigating the causal association between *Helicobacter pylori* (H. pylori) antibodies and immune thrombocytopenia (ITP).[1] While the paper shows an advanced use of MR to address the long-debated link between H. pylori infection and ITP, several methodological and interpretative issues demand further discussion.

Using genetically predicted antibody levels to measure H. pylori infection needs more investigation. My concerns go beyond the authors' brief acknowledgement that their study used genetically predicted antibody levels as a proxy for H. pylori infection. Measuring serum antibody levels might change over time, they may not be a reliable indicator of chronicity or activity of the infection. In addition, antibody levels may stay positive and high after H. pylori eradication. The significant variation in serum antibody levels due to immune status, environmental factors, and individual differences makes them an unreliable marker of infection raising the question of how genetically predicted levels, which do not directly measure exposure, can serve as a true indicator. The actual relationship between H. pylori exposure and ITP risk may be distorted by such measurement error, which could result in misclassification bias. Despite mentioning this limitation, the report doesn't examine how measurement error could quantitatively impact the MR estimations or how future research could address these problems. I believe that a more detailed treatment of this limitation is essential, as it directly affects the interpretation of the causal link presented in the study.

In Chen et al. report, a relaxed selection criterion is used by reducing the significance threshold. Using a higher p-value has the potential of increasing the risk of weak instrument bias, as SNPs with less robust associations to H. pylori antibody levels are included. While such a relaxed criterion was mentioned in the limitation of the study, our critique emphasizes that this relaxation is not merely a minor concession but a critical methodological choice with substantial implications that induces bias. Such a bias could have attenuated the validity of the causal estimates and confounded the observed association between GroEL antibodies and ITP. The potential impact on the study's causal inferences should have been more thoroughly addressed, perhaps by validating the chosen instruments in an independent dataset or by discussing sensitivity analyses specifically designed to quantify the impact of weak instruments.

Furthermore, the imbalance in sample sizes - 605 ITP cases versus over 300,000 controls - although beneficial for statistical power, may mask heterogeneity within the ITP cohort. A more balanced design might have provided additional insights into the variability of ITP presentation and its relationship with H. pylori antibody levels.

Residual confounding may still exist even with strong sensitivity analyses like MR-Egger regression and leave-one-out testing, especially in a condition as complicated as ITP. My concerns center on the multiple etiology of ITP, even though the authors state in passing that pleiotropy was evaluated for and found to be non-significant. Genetic, environmental, and immunological variables interact intricately in the immune mechanisms causing ITP.

This critique emphasizes that while the authors suggest potential clinical benefits, these claims should be tempered by the methodological limitations discussed. A more nuanced discussion on the potential risks, benefits, and clinical applicability of these findings is essential for guiding future therapeutic strategies.

In summary, while Chen et al. have made a commendable effort in applying Mendelian randomization to explore the association between H. pylori antibodies and ITP, several limitations warrant further emphasis and investigation.

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