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LETTER

Enhancing the Robustness of MR Analysis on OSA and Migraine: Addressing Key Limitations [Letter]

Xin Wu, Lizhu Liang, Zheng Wei

Department of Traditional Chinese Medicine, Deyang People's Hospital, Deyang, Sichuan, People's Republic of China

Correspondence: Zheng Wei, Deyang People's Hospital, Deyang, People's Republic of China, Email 1390763659@qq.com

Dear editor

We carefully reviewed the article by Wang et al, which utilized bidirectional Mendelian randomization (MR) to explore the potential causal relationship between obstructive sleep apnea (OSA) and migraine.[1] While this study provides valuable insights into the connection between these two conditions, there are several limitations within the article that warrant further discussion.

First, Figure 3 of the study presents the odds ratio (OR) of migraine without aura (MoA) on OSA, where the beta value obtained using the MR-Egger method is negative, while the beta values from IVW and weighted median methods are positive. This inconsistency in results suggests significant discrepancies between the MR-Egger method and the other methods, which may undermine the validity of the causal inference. One of the fundamental requirements of Mendelian randomization is that the beta values derived from different methods (eg, IVW, MR-Egger, and weighted median) should be consistent in direction. In other words, the results should exhibit a uniform trend, either all positive or all negative. The directional inconsistency of the beta values indicates potential bias in the MR-Egger results, which compromises the reliability of the study's conclusions.

Second, while the authors considered body mass index (BMI) as a potential confounder, the article does not delve into other environmental and behavioral factors that may influence the relationship between OSA and migraine. For instance, lifestyle factors such as smoking, alcohol consumption, and physical activity, or comorbidities like depression and hypertension could significantly impact the occurrence of OSA and migraine.[2,3] Incorporating these factors into a multivariable Mendelian randomization (MVMR) analysis would provide a more comprehensive assessment of their role in the OSA–migraine relationship, thereby enhancing the accuracy and completeness of the study's findings.

Third, there may be a sample overlap issue between the exposure (OSA) and outcome (migraine) datasets used in the study. Specifically, the OSA data comes from the study by Sakaue et al, which includes summary data from the UK Biobank and the FinnGen consortium, while the migraine outcome data is entirely derived from the FinnGen consortium. This sample overlap could lead to significant bias in the MR analysis results.[4] To address this issue, we recommend using completely independent datasets for OSA and migraine or employing statistical methods to correct for sample overlap. For example, utilizing the UK Biobank (UKB) OSA GWAS summary statistics (ukb-d-G6_SLEEPAPNO) would ensure the independence of the two datasets. Additionally, applying the MRLap method,[5] which adjusts for linkage disequilibrium across traits by correcting the regression intercept, could further strengthen the robustness of the study's findings. By adjusting for the impact of overlapping samples, this method allows for a more accurate estimation of the causal effect of exposure on outcomes, thereby enhancing the scientific rigor and credibility of the research.

In conclusion, while this study offers valuable insights into the relationship between OSA and migraine, addressing the aforementioned limitations would further improve the robustness and generalizability of the findings. We commend the authors for their work and look forward to future research that expands upon these preliminary discoveries.

Data Sharing Statement

No new data was generated for this communication.

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