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LETTER

Enhancing the Rigor of Mendelian Randomization: Methodological Insights from the Study on Obstructive Sleep Apnea and Temporomandibular Disorders [Letter]

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Dear editor

We were interested to read the article by Wang et al titled "Causal Relationship Between Obstructive Sleep Apnea and Temporomandibular Disorders: A Bidirectional Mendelian Randomization Analysis"[1]. This study employs a bidirectional Mendelian randomization (MR) approach to explore the genetic causal relationship between obstructive sleep apnea (OSA) and temporomandibular disorders (TMD), offering valuable insights. However, we would like to raise several important considerations and suggestions for the authors.

Firstly, the OSA and TMD data in this study were both sourced from the FinnGen database, which raises concerns about potential sample overlap between the exposure and outcome datasets. In MR studies, such overlap can introduce bias, significantly distorting MR analysis results, including issues related to winner's curse and weak instrument bias.[2] To mitigate this problem, we recommend utilizing completely independent datasets for OSA and TMD or implementing statistical corrections for sample overlap. For instance, external GWAS summary statistics from different cohorts (GWAS ID: ukb-d-G6_SLEEPAPNO) could be employed to ensure the independence of the two datasets. Additionally, the use of the MR-Lap method,[3] which adjusts for linkage disequilibrium scores through regression intercepts, has shown good fit in simulations with 5% to 95% overlap, thus enhancing the robustness of the study's findings.

Secondly, the authors did not adjust for potential confounders such as body mass index, smoking status,[4] alcohol consumption,[4] and psychological stress, which may lead to pleiotropic effects, as these factors are known to influence both OSA and TMD. While the authors employed MR-Egger and MR-PRESSO methods to detect horizontal pleiotropy, these approaches may not fully eliminate the effects of confounding pathways that could bias the results. Conducting a more thorough analysis using multivariable Mendelian randomization (MVMR) could be beneficial,[5] as it allows for the inclusion of additional genetic variants that may help adjust for pleiotropic effects and improve the reliability of the results.

In summary, the study by Wang et al makes significant contributions to our understanding of the relationship between OSA and TMD; however, caution is warranted in interpreting the results. Addressing issues of sample overlap and confounding factors could further strengthen the evidence and enhance the clinical significance of the findings. Therefore, we encourage the authors to consider these limitations in their future research and take measures to eliminate or correct for sample overlap, leading to more reliable conclusions.

Author Contributions

Zhangbing Zhou: Methodology, Formal analysis, Writing - Original Draft; Liu Wang: Methodology, Writing - Original Draft; Yunfeng Chen: Conceptualization, Methodology, Supervision, Writing - Review & Editing.

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References

1. Wang Y-P, Wei H-X, Hu -Y-Y, Niu Y-M. Causal relationship between obstructive sleep apnea and temporomandibular disorders: A bidirectional Mendelian randomization analysis. *Nat Sci Sleep*. 2024;16(2024):1045–1052. doi:10.2147/NSS.S476277
2. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol*. 2016;40 (2016):597–608. doi:10.1002/gepi.21998
3. Mounier N, Kutalik Z. Bias correction for inverse variance weighting Mendelian randomization. *Genet Epidemiol*. 2023;47(2023):314–331. doi:10.1002/gepi.22522
4. Miettinen O, Anttonen V, Patinen P, et al. Prevalence of temporomandibular disorder symptoms and their association with alcohol and smoking habits. *J Oral Facial Pain Head*. 2017;31(2017):30–36. doi:10.11607/ofph.1595
5. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol*. 2015;181(2015):251–260. doi:10.1093/aje/kwu283

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