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LETTER

A Comprehensive Mendelian Randomization Study of Bidirectional Causal Relationships Between Pain and Mental Disorders [Letter]

Jing Han[1], Yifan Ye[1], Yuying Mao[1], Liming Lou[2]

[1]The Third Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [2]The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Liming Lou, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310005, People's Republic of China, Tel +8613505712348, Email loulim1006@163.com

Dear editor

We read with great interest the article by Liang and Fan entitled "A Comprehensive Mendelian Randomization Study of Bidirectional Causal Relationships Between Pain and Mental Disorders," recently published in the Journal of Pain Research.[1] Using bidirectional Mendelian randomization (MR) combined with multivariable MR approaches, the authors investigated potential causal relationships between multiple pain phenotypes and a wide range of mental and personality disorders. By integrating several large genome-wide association study (GWAS) datasets and incorporating adjustments for potential confounders such as obesity, insomnia, and substance use, the study provides valuable genetic evidence supporting the complex bidirectional interaction between pain and psychiatric conditions. The authors should be commended for their comprehensive analytical framework and for extending MR investigations beyond commonly examined conditions such as depression and anxiety. Nevertheless, several methodological considerations may help further contextualize the interpretation of these findings.

First, the definition of several pain phenotypes may introduce heterogeneity that could influence causal inference. In particular, many exposure variables—especially the "recent pain" traits—were derived from self-reported questionnaire data within the UK Biobank. While this approach enables large-scale population analysis, self-reported pain is inherently subjective and may be influenced by recall bias, individual pain perception, and psychological status. The authors correctly identified the use of binary phenotype definitions as an important limitation. The available GWAS datasets lacked detailed information regarding pain intensity, pain chronicity, functional impairment, and severity of psychiatric symptoms. Consequently, the reported causal estimates may not fully capture the heterogeneity of clinical pain experiences or mental disorders. Future investigations incorporating more refined phenotypic characterization may provide additional insights into whether causal effects vary according to disease severity or symptom burden.[2]

Second, we commend Liang and Fan for their rigorous assessment of horizontal pleiotropy. They employed multiple complementary methods—including MR-Egger (intercept test), MR-PRESSO (outlier detection and correction), weighted median estimation, and leave-one-out analyses—and found no evidence of directional pleiotropy. This comprehensive approach substantially mitigates concerns that pleiotropy might drive their findings. As a forward-looking suggestion for future MR studies in pain-psychiatry research, we note that newer methods such as MR-RAPS (robust adjusted profile score)[3] and contamination mixture models can provide additional robustness against both weak instruments and balanced pleiotropy, and may be considered when even more stringent control is desired. However, we emphasize that this is a suggestion for future methodological refinement, not a criticism of the original authors' already-thorough analysis.

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Third, the selection threshold for instrumental variables warrants consideration. In this study, single nucleotide polymorphisms were selected using a genome-wide significance threshold of $P < 5\times10^{-6}$.Although Liang and Fan selected instrumental variables using a relaxed genome-wide significance threshold of $P < 5\times10^{-6}$, they subsequently demonstrated that all instrumental variables exhibited F-statistics exceeding 10, thereby eliminating the concern of weak instrument bias.We acknowledge that the original authors have already addressed this issue appropriately. Nevertheless, for future MR studies employing similarly relaxed selection thresholds, we suggest that reporting mean F-statistics or the proportion of variance explained for each exposure trait—as the original authors did—should be considered a best practice to enhance transparency.

Fourth, the statistical power for several exposure–outcome pairs may be limited due to relatively small case numbers for certain psychiatric and personality disorders included in the analysis, such as histrionic personality disorder, paranoid personality disorder, and trigeminal neuralgia.We commend Liang and Fan for their transparent discussion of statistical power limitations, including the low power for trigeminal neuralgia (46%) and the inherent trade-off between Type I and Type II errors under Bonferroni correction. By explicitly presenting a power heatmap (their Figure 7) and acknowledging that "multiple testing corrections … might also increase Type II errors," the authors have set a commendable standard for reporting in exploratory MR studies. Building on their work, future studies with larger GWAS samples for rarer personality disorders (eg., histrionic, paranoid) and replication cohorts will be essential to determine whether the nominally significant but Bonferroni-non-significant associations represent true effects or false negatives.[4]

Beyond these methodological considerations, the present study raises important questions regarding the biological mechanisms underlying the observed bidirectional relationships between pain and mental disorders. Increasing evidence indicates that pain processing and emotional regulation share overlapping neural circuits, particularly within the prefrontal cortex, anterior cingulate cortex, and limbic structures.[5–7]Integrating genetic findings with neuroimaging, transcriptomic, or multi-omics data may provide deeper insight into the shared biological pathways linking pain and psychiatric disorders. Furthermore, extending similar analyses to populations with diverse ancestral backgrounds would improve the generalizability of these findings beyond individuals of European descent.

In conclusion, Liang and Fan provide an important contribution by systematically examining the bidirectional genetic relationships between multiple pain phenotypes and a broad spectrum of psychiatric conditions. Addressing issues related to phenotype definition, pleiotropic pathways, instrumental variable selection, and statistical power in future studies may further strengthen the interpretation and clinical implications of this work.

Disclosure

The authors report no conflicts of interest in this communication.

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