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No Causal Association between Insomnia and Gout: A Bidirectional Two-Sample Mendelian Randomization Study

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Abstract: Purpose: Previous observational studies have suggested an association between insomnia and gout. However, the causal nature of this relationship remains uncertain. This study aimed to investigate the bidirectional causal association between insomnia and gout using a Mendelian randomization (MR) analysis. **Methods:** A bidirectional two-sample MR analysis was conducted utilizing genome-wide association study (GWAS) summary data for insomnia and gout. Single-nucleotide polymorphisms (SNPs) significantly associated with insomnia and gout were used as instrumental variables. Causal effects were estimated using the inverse variance weighted (IVW) method, MR-Egger, and weighted median. Sensitivity analyses were then performed to assess potential pleiotropy and heterogeneity. **Results:** The MR analysis revealed no significant causal relationship between insomnia and the risk of gout (IVW OR=1.300, 95%CI:0.566-2.986, P=0.537). Similarly, reverse MR analysis showed no causal effect of gout on the risk of insomnia (IVW OR=1.005, 95%CI:0.999-1.011, P=0.099). The findings were consistent across all sensitivity analyses, with no evidence of horizontal pleiotropy or heterogeneity (P>0.05). **Conclusion:** This study found no evidence supporting a causal relationship between insomnia and gout in either direction. These findings suggest that previous associations observed in observational studies might be confounded by other factors. Further research using larger sample sizes and diverse populations is warranted to validate these results.

Keywords: Genetic Variants; Insomnia; Gout; Risk Factors.

1. Introduction

Gout is a chronic inflammatory arthritis characterized by sudden, intense joint pain, swelling, and redness [1]. It results from the deposition of monosodium urate crystals due to prolonged hyperuricemia. Globally, gout affects millions of people, and its prevalence has been steadily rising over the past few decades, particularly in developed countries [2-3]. This condition is associated with a range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome, further amplifying its impact on global health [4]. Effective management of gout requires a comprehensive understanding of its risk factors, which traditionally include genetic predisposition, dietary habits, obesity, and alcohol consumption [5].

Insomnia is one of the most prevalent sleep disorders, affecting approximately 10% of adults worldwide [6]. It is characterized by difficulties in falling asleep, staying asleep, or waking up too early, leading to significant impairments in daily functioning. Chronic insomnia is associated with a range of adverse health outcomes, including cardiovascular diseases, metabolic disorders, mental health issues, and reduced quality of life [7]. Despite its substantial impact on global health, the underlying causes of insomnia remain not fully understood. Traditionally, research has focused on psychological and environmental triggers; however, recent studies suggest that physiological processes, such as inflammation and metabolic dysregulation, may also play a role [8-9].

Given the rising prevalence of both gout and insomnia, along with their increasing burden on public health, there is growing interest in exploring the potential relationship between these two conditions. Some observational studies suggest that insomnia may exacerbate inflammatory responses and metabolic disturbances, potentially influencing the progression of diseases such as gout [10]. Conversely, the intense pain and discomfort associated with gout flares may disrupt sleep, leading to the development of insomnia [11]. However, there are also studies that have not found a significant association between insomnia and gout [12]. These conflicting findings may partly be due to the limitations of cross-sectional study designs, which cannot establish causality and may be influenced by confounding factors. Therefore, it is crucial to further clarify the relationship between insomnia and gout to better understand their potential interplay.

With the continuous advancements in genetic epidemiology, several novel research methodologies have emerged, particularly Mendelian randomization (MR) analysis [13-14]. MR analysis provides a robust framework for investigating potential causal relationships between risk factors and diseases. It is grounded on three key assumptions: first, the genetic variants used as instrumental variables are strongly associated with the exposure of interest; second, these genetic variants are independent of any potential confounders; and third, the genetic variants affect the disease outcome solely through their influence on the exposure [15-16]. Based on these assumptions, MR analysis can effectively mitigate the influence of confounding factors and reverse causation [17]. Thus, MR analysis holds significant value in determining causal links between risk factors and diseases.

The aim of this study is to estimate the causal relationship

between insomnia and gout by conducting a bidirectional two-sample MR analysis.

2. Material and Methods

2.1. Summary Statistics Data for Insomnia and Gout

The summary genome-wide association study (GWAS) data for insomnia and gout were directly or indirectly obtained from the IEU Open GWAS project (https:// gwas. mrcieu. ac.uk/). The insomnia dataset (ukb-a-13) includes 336,965 individuals of European descent with 10,894,596 Single-nucleotide polymorphisms (SNPs). The gout dataset (finn-b-M13_GOUT) comprises 3,576 cases and 147,221 controls of European ancestry with 16,380,152 SNPs. Importantly, there is no potential sample overlap between these datasets, ensuring the accuracy and reliability of the MR analysis results.

2.2. Selection of Instrumental Variables

Based on the three core assumptions mentioned earlier, we first selected SNPs that are strongly associated with insomnia and gout by applying a genome-wide significance threshold of p<5e-8. To ensure the independence of the selected SNPs, we then performed clumping with parameters set at r^2<0.001 within a 10000-kb window. Additionally, The F-statistics for SNPs were calculated to assess instrument strength ($F = \left(\frac{n-1-k}{k}\right) \times \frac{R^2}{1-R^2}$), where n represents the sample size, k represents the number of genetic variants, and R^2 denotes the proportion of phenotypic variance explained by the genetic variants. All instrumental variables used in this study had F-statistics greater than 10, thereby avoiding weak instrument bias.

2.3. Bidirectional Mendelian Randomization Analysis

A bidirectional two-sample MR analysis was conducted to explore the potential causal relationships between insomnia and gout [18-19]. The primary MR analysis used the inverse variance weighted (IVW) method to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To ensure the robustness of the findings, additional MR methods, including MR-Egger and the weighted median, were employed. The analysis was performed in two directions: first, to assess whether genetic predisposition to insomnia influences the risk of developing gout, and second, to evaluate whether a genetic predisposition to gout influences the risk of developing insomnia.

2.4. Statistical Methods

Sensitivity analyses were conducted to evaluate the reliability and validity of the MR results. Both MR-Egger intercept and Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global tests were used to identify and correct for horizontal pleiotropy, with P>0.05 in these tests indicating no significant pleiotropic effect [20-21]. Heterogeneity among instrumental variables was assessed using Cochrane's Q test, where P>0.05 suggested no significant heterogeneity [22-23]. Additionally, a leave-one-out analysis was performed to determine the influence of individual SNPs on the overall causal estimates [24]. All MR analyses were conducted using the "TwoSampleMR" packages in R.

3. Results

The bidirectional MR analysis revealed no significant causal relationship between genetically predicted insomnia and gout (IVW OR=1.300, 95%CI:0.566-2.986, P=0.537) (Figures 1). Similarly, the reverse MR analysis showed no causal association between genetically predicted gout and insomnia (IVW OR=1.005, 95%CI:0.999-1.011, P=0.099) (Figures 2).

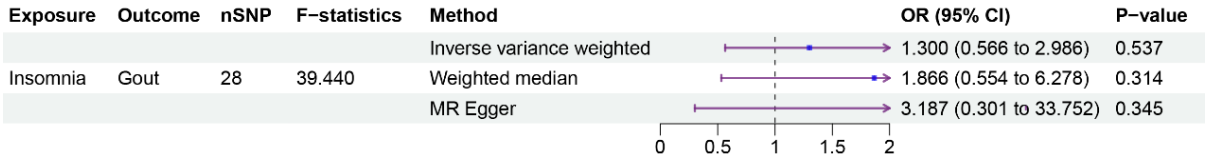

Figure 1. MR estimates of insomnia on the risk of gout.

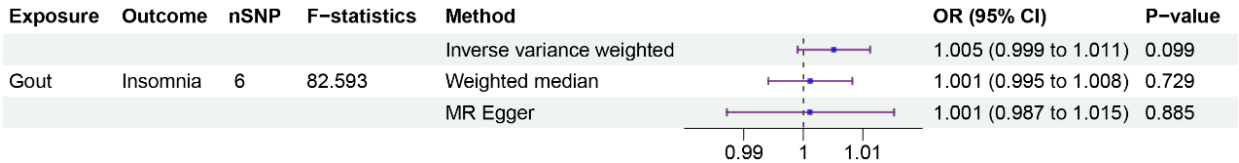

Figure 2. MR estimates of gout on the risk of insomnia.

The sensitivity analyses, as presented in Table 1, showed no significant heterogeneity among the genetic instruments according to Cochran's Q test (P>0.05). Additionally, both the MR-Egger intercept test and the MR-PRESSO global test found no evidence of significant pleiotropy (P>0.05).

Table 1. The heterogeneity and horizontal pleiotropy of MR and reverse MR.

Exposure	Outcome	Heterogeneity P	MR-Egger intercept P	MR-PRESSO P
Insomnia	Gout	0.603	0.433	0.604
Gout	Insomnia	0.316	0.563	0.365

The leave-one-out analysis demonstrated that excluding each SNP one at a time and recalculating the causal estimates did not significantly alter the overall MR estimates (Figures 3). This confirms that the results are not driven by any specific

SNP.

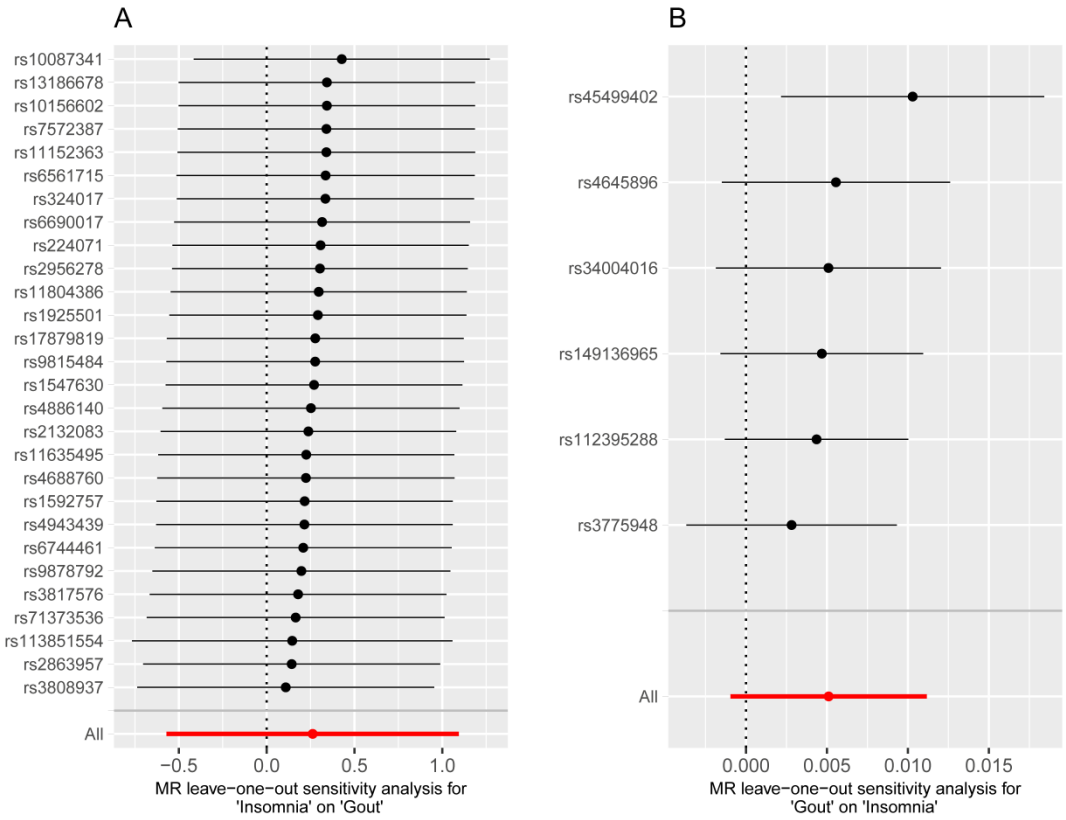

Figure 3. Leave-one-out plots of bidirectional causal estimates between insomnia and gout

4. Discussion

This bidirectional MR analysis found no causal relationship between insomnia and gout, challenging the findings of several observational studies that have reported associations between sleep disturbances and gout. These studies often suggest that poor sleep quality or sleep disorders, such as insomnia and obstructive sleep apnea (OSA), are more prevalent among individuals with gout, implying a potential link mediated by shared metabolic and inflammatory pathways [25-26].

For example, an Internet-based cross-sectional survey highlights that individuals with gout frequently report sleep disturbances. In this study, nearly a quarter of participants with gout reported having sleep disorders, with insomnia and OSA being the most common [11]. Similarly, other studies have found a higher prevalence of insomnia among gout patients, proposing that the presence of sleep disturbances and gout may be interlinked through shared mechanisms such as metabolic dysregulation, chronic inflammation, and oxidative stress [10,27]. These findings have triggered hypotheses about shared pathophysiological mechanisms, such as oxidative stress and inflammation, potentially linking the two conditions.

However, certain limitations in these observational studies might affect the validity of the associations between insomnia and gout. First, some studies rely on specific cohorts, such as clinic patients or online survey respondents, which could introduce selection bias, particularly if individuals with more severe symptoms or greater health awareness are overrepresented. This could lead to an overestimation of the association between insomnia and gout. Second, both insomnia and gout are associated with confounding factors, such as obesity, alcohol consumption, and hypertension, which are challenging to fully adjust for in observational studies and may exaggerate the observed associations. Finally, the use of self-reported data further introduces reporting bias, complicating the interpretation of these findings.

Notably, a study using an animal model found that pain from gout flares increases wakefulness and reduces both the duration and frequency of Rapid Eye Movement (REM) sleep, without affecting slow-wave sleep. These results suggest that the immediate effects of gout flares may cause temporary sleep disturbances rather than indicating a direct causal relationship with chronic insomnia or other persistent sleep disorders [12]. This aligns with our MR study findings, which also suggest that there is no direct causal link between insomnia and gout. By using genetic variants as instrumental variables, our MR analysis minimizes confounding and avoids reverse causation, providing stronger evidence that the associations observed in prior observational studies are likely due to shared risk factors or comorbidities, rather than a direct pathophysiological connection [28]. This understanding is important for clinical practice, indicating that a focus on managing shared risk factors, such as obesity, diet, and metabolic health, may be more effective than targeting insomnia alone in reducing the risk of gout.

It should be noted that, despite the strengths of our MR analysis, our study has limitations. First, the analysis is mainly based on populations of European descent, limiting the generalizability to other ethnic groups. The genetic factors related to insomnia and gout may vary across populations, so future studies should include more diverse cohorts. Second, our findings depend on the quality and availability of GWAS data. Larger, more comprehensive GWAS datasets are needed to enhance the power of MR analyses, particularly for

complex traits like insomnia and gout.

5. Conclusion

In conclusion, this bidirectional MR analysis indicates that there is no direct causal relationship between insomnia and gout, contrasting with conclusions drawn from previous observational studies. This suggests that focusing on shared risk factors may be more appropriate than assuming a direct causal link.

Data Sharing Statement

This study utilized publicly available datasets for analysis. The original contributions made to the research are outlined in the article; for additional inquiries, please contact the corresponding author.

Ethics Approval

Since all data used in this study were obtained from publicly available databases, no additional ethical approval or patient consent was required.

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The authors declare that there are no financial or non-financial interests that could have influenced the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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References

[1] Marotto D, De Santis A, Chessa D, Firinu D, Del Giacco S. A Beacon in the Dark: Canakinumab. A New Therapeutic Perspective in Chronic Tophaceous Gout. Rheumatol Ther. 2018;5(1):303-310. doi:10.1007/s40744-018-0104-8.

[2] Chandratre P, Mallen C, Richardson J, et al. Health-related quality of life in gout in primary care: Baseline findings from a cohort study [published correction appears in Semin Arthritis Rheum. 2022 Feb;52:151800. doi: 10.1016/j.semarthrit. 2021. 02.009]. Semin Arthritis Rheum. 2018;48(1):61-69. doi:10. 1016/j. semarthrit.2017.12.005.

[3] Shi C, Zhou Z, Chi X, et al. Recent advances in gout drugs. Eur J Med Chem. 2023;245(Pt 1):114890. doi:10.1016/j. ejmech. 2022. 114890.

[4] Choi HK, McCormick N, Yokose C. Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care. Nat Rev Rheumatol. 2022;18(2):97-111. doi:10.1038/s41584-021-00725-9.

[5] Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol. 2011;23(2):192-202. doi:10.1097/BOR. 0b013 e32 83438e13.

[6] Riemann D, Dressle RJ, Benz F, et al. Chronic insomnia, REM sleep instability and emotional dysregulation: A pathway to anxiety and depression?. J Sleep Res. Published online May 29, 2024. doi:10.1111/jsr.14252.

[7] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems [published correction appears in Sleep. 2007 Jul 1;30 (7): table of contents]. Sleep. 2007;30(2):213-218. doi:10. 1093/ sleep/30.2.213.

[8] Chami HA, Bechnak A, Isma'eel H, et al. Sleepless in Beirut: Sleep Difficulties in an Urban Environment With Chronic Psychosocial Stress. J Clin Sleep Med. 2019;15(4):603-614. Published 2019 Apr 15. doi:10.5664/jcsm.7724.

[9] Wang Q, Chen B, Sheng D, et al. Multiomics Analysis Reveals Aberrant Metabolism and Immunity Linked Gut Microbiota with Insomnia. Microbiol Spectr. 2022;10(5):e0099822. doi: 10. 1128/spectrum.00998-22.

[10] Wu Q, He P, Ye Z, et al. Sleep patterns, genetic susceptibility, and risk of new-onset gout: The UK Biobank prospective cohort study. J Psychosom Res. 2023;170:111381. doi: 10. 1016/ j. jpsychores.2023.111381.

[11] Singh JA. Self-reported sleep quality and sleep disorders in people with physician-diagnosed gout: an Internet cross-sectional survey. Arthritis Res Ther. 2019;21(1):36. Published 2019 Jan 25. doi:10.1186/s13075-019-1821-2.

[12] Guevara-López U, Ayala-Guerrero F, Covarrubias-Gómez A, López-Muñoz FJ, Torres-González R. Effect of acute gouty arthritis on sleep patterns: a preclinical study. Eur J Pain. 2009;13(2):146-153. doi:10.1016/j.ejpain.2008.04.002.

[13] Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. JAMA. 2017;318(19):1925-1926. doi: 10. 1001/ jama.2017.17219.

[14] Richmond RC, Davey Smith G. Mendelian Randomization: Concepts and Scope. Cold Spring Harb Perspect Med. 2022;12(1):a040501. Published 2022 Jan 4. doi:10.1101/ cshperspect. a040501.

[15] Nguyen K, Mitchell BD. A Guide to Understanding Mendelian Randomization Studies. Arthritis Care Res (Hoboken). Published online July 19, 2024. doi:10.1002/acr.25400.

[16] Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. Nat Rev Methods Primers. 2022;2:6. doi:10. 1038/ s43586-021-00092-5.

[17] Evans DM, Davey Smith G. Mendelian Randomization: New Applications in the Coming Age of Hypothesis-Free Causality. Annu Rev Genomics Hum Genet. 2015;16:327-350. doi:10.1146/annurev-genom-090314-050016.

[18] Lloyd K, Harrison S, Sallis HM, Davey Smith G, Munafò MR, Wootton RE. Exploring the Bidirectional Causal Pathways Between Smoking Behaviors and Headache: A Mendelian Randomization Study. Nicotine Tob Res. 2024;26(7):903-912. doi:10.1093/ntr/ntad173.

[19] Xu S, Gilliland FD, Conti DV. Elucidation of causal direction between asthma and obesity: a bi-directional Mendelian randomization study. Int J Epidemiol. 2019;48(3):899-907. doi:10.1093/ije/dyz070.

[20] Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method [published correction appears in Eur J Epidemiol. 2017 May;32(5):391-392. doi: 10.1007/s10654-017-0276-5]. Eur J Epidemiol. 2017;32(5):377-389. doi:10.1007/s10654-017-0255-x.

[21] Ong JS, MacGregor S. Implementing MR-PRESSO and GCTA-GSMR for pleiotropy assessment in Mendelian randomization studies from a practitioner's perspective. Genet Epidemiol. 2019;43(6):609-616. doi:10.1002/gepi.22207.

[22] Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. Epidemiology. 2017;28(1):30-42. doi:10.1097/EDE. 0000000000000559.

[23] Xue H, Liu S, Zeng L, Fan W. Causal effect of systemic lupus erythematosus on psychiatric disorders: A two-sample Mendelian randomization study. J Affect Disord. 2024; 347: 422-428. doi:10.1016/j.jad.2023.11.033.

[24] Du W, He K, Liu X, Yin T, Xiao S, Zheng Y. Genetic association between asthma and alopecia areata: A two-sample Mendelian randomization study. Skin Res Technol. 2024;30(7): e13844. doi:10.1111/srt.13844.

[25] Paulsamy P, Venkatesan K, Alshahrani S, et al. Alternate Warm and Cold Therapy (AWCT) on Uricemia, Sleep, Pain, Functional Ability, and Quality of Life (USPFQoL) in Patients with Gout: A Path Forward. J Healthc Eng. 2022;2022: 5471 575. Published 2022 Mar 9. doi:10.1155/2022/ 5471575.

[26] New-Tolley J, Reynolds AC, Appleton SL, et al. Sleep disorders and gout in Australian adults. BMC Rheumatol. 2021; 5(1):30. Published 2021 Aug 28. doi:10.1186/s41927-021-00199-y.

[27] Augusto Ferreira de Andrade C. Assessing qualitatively the impact of gout on sleep: any sleep was a dream far away until the gout flare resolved. Rheumatology (Oxford). 2018;57 (11): 1877-1878. doi:10.1093/rheumatology/key184.

[28] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. J Am Soc Nephrol. 2016;27(11):3253-3265. doi:10.1681/ASN.2016010098.