Causal relationship between sleep traits and erectile dysfunction: Evidence from Mendelian Randomization analysis

Keywords
insomnia, chronotype, Erectile dysfunction, Mendelian randomization, snoring, short sleep

Abstract

Introduction

Although several observational studies have explored the association between sleep traits and the risk of erectile dysfunction (ED), it remains controversial. In the present study, we included a wide range of sleep traits that are commonly observed in clinical practice. We investigated the causal relationship between these sleep traits and ED using univariate and multivariate Mendelian randomization (MR) methods.

Material and methods

Instrumental variables (IVs) for eight sleep traits (insomnia, sleep duration, chronotype, and sleep apnea syndrome), five confounders (depression, body mass index, smoking initiation, alcohol consumption, and type 2 diabetes), and ED were derived from genome-wide association study (GWAS) data of individuals of European ancestry. The primary analysis technique used was the inverse-variance weighted (IVW) approach. Furthermore, several sensitivity analyses were conducted to evaluate heterogeneity, horizontal pleiotropy, and stability.

Results

MR analysis revealed that increased snoring, short sleep, and frequent insomnia, were associated with a higher risk of ED. Furthermore, we found evidence of a significant association between being a morning person and the risk of developing ED. This association persisted in multivariable MR analyses after adjusting for potential confounding factors. Sensitivity analysis suggested that the results were robust with no evidence of pleiotropy or heterogeneity.

Conclusions

This study provides further evidence supporting the association between genetically predicted snoring, insomnia, and an increased risk of ED. Additionally, the study highlights the causal relationship of short sleep duration and chronotype with ED.

Preprint

Causal relationship between sleep traits and erectile dysfunction: Evidence from Mendelian Randomization analysis

Abstract

Introduction: Although several observational studies have explored the association between sleep traits and the risk of erectile dysfunction (ED), it remains controversial. In the present study, we included a wide range of sleep traits that are commonly observed in clinical practice. We investigated the causal relationship between these sleep traits and ED using univariate and multivariate Mendelian randomization (MR) methods.

Material and Methods: Instrumental variables (IVs) for eight sleep traits (insomnia, sleep duration, chronotype, and sleep apnea syndrome), five confounders (depression, body mass index, smoking initiation, alcohol consumption, and type 2 diabetes), and ED were derived from genome-wide association study (GWAS) data of individuals of European ancestry. The primary analysis technique used was the inverse-variance weighted (IVW) approach. Furthermore, several sensitivity analyses were conducted to evaluate heterogeneity, horizontal pleiotropy, and stability.

Results: MR analysis revealed that increased snoring, short sleep, and frequent insomnia, were associated with a higher risk of ED. Furthermore, we found evidence of a significant association between being a morning person and the risk of developing ED. This association persisted in multivariable MR analyses after adjusting for potential confounding factors. Sensitivity analysis suggested that the results were robust with no evidence of pleiotropy or heterogeneity.

Conclusions: This study provides further evidence supporting the association between genetically predicted snoring, insomnia, and an increased risk of ED.

Preprint

Additionally, the study highlights the causal relationship of short sleep duration and chronotype with ED.

Keywords

Erectile dysfunction, snoring, short sleep, insomnia, chronotype, Mendelian randomization

Preprint

Introduction

Erectile dysfunction (ED) is a prevalent global issue which is defined as the persistent inability to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse. The pathogenesis of ED is multifactorial, involving various factors, such as psychogenic (e.g., depression, anxiety, and stress), organic (e.g., aging, obesity, diabetes mellitus, and other conditions), or mixed causes [1]. ED may also be induced by unhealthy lifestyle factors, including smoking, alcohol consumption, insomnia, snoring, and lack of exercise. [2, 3] Numerous clinical studies have confirmed that adopting healthy lifestyle changes could serve as an effective strategy to mitigate the risk of ED [4-6].

Adverse sleep patterns have significant public health implications. Numerous studies have investigated the correlation between sleep traits, such as insomnia and obstructive sleep apnea (OSA), and the risk of ED [7-9]. A large cross-sectional observational study conducted in the Chinese population supports the findings of a Taiwanese population-based cohort study. The study revealed that patients with OSA had a significantly higher incidence of ED [10, 11]. During a 3-year follow-up period involving 539,109 men with insomnia, both untreated and treated insomnia were associated with an increased risk of ED [7]. The results of monitoring sleep quality in patients with ED showed that both total sleep time and duration of deep sleep were significantly lower than those in the non-ED group [12]. However, traditional observational studies are greatly influenced by factors such as sample size, confounding variables, and reverse causation.

The Mendelian randomization (MR) study is a research technique that investigates the causal relationship between exposure and outcome, similar to that of randomized controlled trials [13]. Single-nucleotide polymorphisms (SNPs) that exhibited a strong

Preprint

correlation with exposure were used as instrumental variables (IVs) to determine the presence of a causal relationship between exposure and outcome in MR studies. The objective of this study was to estimate the causal relationship between sleep traits and ED using a two-sample MR study.

Material and methods

Study design overview

We conducted a two-sample MR analysis using publicly available data from genome-wide association studies (GWAS). This study included sleep traits, such as insomnia, sleep duration, morning chronotype, snoring, and OSA. The MR approach relies on three crucial assumptions: (1) the IVs should have a strong association with exposure; (2) the IVs should not be associated with any confounding factors; and (3) the IVs should only influence the outcome through exposure.

Data Sources for sleep traits, ED, and potential confounders

Sleep duration [14]**:** Summary-level information on sleep duration, including short sleep (≤6 h/day) and long sleep (≥9 h/day), was acquired from the GWAS data of 446,118 individuals of European ancestry. The data analysis included 106,192 cases with short sleep duration and 305,742 controls, as well as 34,184 cases with long sleep duration and 305,742 controls (**Table 1**).

Insomnia: Summary-level information on insomnia was acquired from GWAS data of 453,379 individuals of European ancestry [15] (345,022 cases with frequent insomnia and 108,357 controls) and GWAS data of 1,331,010 individuals of European ancestry [16] (109,389 cases with any insomnia and 277,144 controls) (**Table 1**).

Morning person [15]**:** Summary-level information on morning chronotypes was acquired from the GWAS data of 449,734 individuals of European ancestry. This

Preprint

dataset included 252,287 cases of morning chronotypes and 150,908 controls (**Table 1**).

Snoring [17]**:** Summary-level information on snoring was acquired from the GWAS data of 408,317 individuals of European ancestry. Within this dataset, 152,302 snoring cases and 256,015 controls were included (**Table 1**).

Sleep apnea syndrome [18]**:** Summary-level information on sleep apnea syndrome was acquired from the GWAS data of 476,853 individuals of European ancestry. This dataset included 13,818 patients with sleep apnea symptoms and 463,035 healthy controls (**Table 1**).

ED [19]**:** Summary-level information on ED was acquired from the GWAS data of 223,805 individuals of European ancestry. The study included 6,175 patients with ED and 217,630 controls (**Table 1**).

Potential confounders: To account for potential genetic confounders associated with sleep traits, such as depression [20], type 2 diabetes mellitus (T2DM) [21], body mass index (BMI) [22], smoking [23], and alcohol consumption [23], we investigated the direct effect of certain sleep traits on ED using a multivariate MR approach by adjusting for these factors. Summary-level information on these factors is provided in **Table 1**.

Further information on the diagnostic criteria for exposures and outcomes can be obtained from the abovementioned literature.

Selection of instrumental variables

In the first MR analysis, IVs were used based on a genome-wide significance threshold ($P < 5e{-}8$) to estimate the causal effect of sleep traits on ED risk. In the second MR analysis, IVs screened using a locus-wide significance threshold ($P < 1e{-}5$) were evaluated to determine the causal effect of sleep traits on ED risk. SNPs

Preprint

within a 10,000 kb window were eliminated based on a threshold of $r^2 < 0.001$, to alleviate the effects of linkage disequilibrium (LD). Then, the strength of the IVs was assessed using *F*-statistics, which were calculated according to the formula $F = R^2 \times (N - 2) / (1 - R^2)$, where R^2 represents the proportion of variance explained and N is the total sample size. The following formula was used to compute R^2: $2 \times EAF \times (1 - EAF) \times beta^2$, where EAF denotes the effect allele frequency, and beta represents the estimated genetic effect on exposure risk. IVs with *F*-statistics > 10 were commonly chosen to reduce the potential bias from weak IVs.

Statistical analyses

This study used four different MR analysis methods: inverse-variance weighted (IVW) [24], MR-Egger [25], weighted median [26], and weighted mode [27]. The IVW method was primarily used for the meta-analysis of the SNP-specific Wald estimates, assuming balanced pleiotropy. The outcomes of the causal relationships were expressed in terms of odds ratios (OR) and 95% confidence intervals (95% CI). Several sensitivity analyses were also performed. First, the significance of the MR-Steiger test results suggested that causal inference was not biased by reverse causation. Otherwise, this indicated the presence of a reverse causal direction. Next, the Cochran's Q test was used to assess heterogeneity. A P value of < 0.05 indicated significant heterogeneity. The random-effects IVW model was used in subsequent analyses. Otherwise, a fixed-effects IVW model was used. Then, the MR-Egger intercept and MR-PRESSO global tests were used to detect any potential pleiotropic effects of the genetic variants on the estimate of causality. Finally, leave-one-out analysis was performed by removing each IV to determine whether the results were disproportionately affected by a single SNP. In multivariate MR analyses, direct causal effects were estimated using the IVW method after adjusting for depression,

Preprint

T2DM, BMI, smoking, and alcohol consumption. The statistical analyses were conducted using R software (v 4.2.1). The MR analysis was conducted using the R packages "Two Sample MR," "Mendelian Randomization," and "'MRPRESSO."

To minimize the occurrence of false positives due to multiple comparisons (eight expsure factors), we used the Benjamini-Hochberg false discovery rate (FDR) correction. P values that passed a critical value corresponding to an FDR of 0.05 were considered strong evidence of associations. P values that did not pass a critical value but were less than 0.05 were considered suggestive evidence of associations.

Results

Results of MR analysis using IVs screened based on genome-wide significance ($P < 5e{-}8$)

MR analysis revealed that increased snoring was associated with an elevated risk of ED (IVW: OR: 4.16, 95% CI: 1.40–12.38, P: 1.04e-2; P_{FDR} = 4.99e-2) (**Supplementary Figure 1**). Furthermore, we found that being a morning person was associated with a lower risk of developing ED (IVW: OR: 0.86, 95% CI: 0.77–0.97, P: 1.25e-2; P_{FDR} = 4.99e-2). However, the results indicated no evidence supporting a potential causal effect of short sleep, long sleep, sleep duration, sleep apnea syndrome, any insomnia, or frequent insomnia on the risk of ED according to the IVW analysis (all $P > 0.05$).

For the sensitivity analysis, **Supplementary Figures 2–4** depict funnel plots, scatter plots, and results of the leave-one-out analysis. The MR-Steiger test results suggested no bias in causal inference due to reverse causation ($P < 0.05$). No heterogeneity was found in the MR analysis, as determined by Cochran's Q test ($P > 0.05$). The MR-Egger intercept test and MR-PRESSO global test indicated that MR analysis was not

Preprint

affected by horizontal pleiotropy (P > 0.05) (**Supplementary Table 1**).

Results of MR analysis using IVs screened based on locus-wide significance (P < 1e−5)

MR analysis revealed that a shorter sleep duration was associated with a higher risk of ED (IVW: OR: 3.02, 95% CI: 1.59–5.77, P: 7.82e-4; P_{FDR} = 6.25e-4) (**Figure 1**). Furthermore, we found that frequent insomnia was a risk factor for ED (IVW: OR: 1.70, 95% CI: 1.14–2.51, P: 8.57e-3; P_{FDR} = 3.43e-2). However, the results showed no evidence of a potential causal effect of long sleep, sleep duration, sleep apnea syndrome, morning person, any insomnia, or frequent insomnia on the risk of ED according to the IVW analysis (all P > 0.05).

Supplementary Figures 5–7 depict funnel plots, scatter plots, and leave-one-out analysis results for the sensitivity analysis. The significance of the MR-Steiger test results suggested that there was no bias in causal inference due to reverse causation (P < 0.05). No heterogeneity was found in the MR analysis, as determined by Cochran's Q test (P > 0.05). The MR-Egger intercept test and MR-PRESSO global test indicated that MR analysis was not affected by horizontal pleiotropy (P > 0.05) (**Table 2**).

Results of the multivariable Mendelian randomization analysis

We conducted multivariate MR analysis to evaluate the direct causal effect of short sleep duration and frequent insomnia on the risk of ED. This analysis considered five confounding factors: depression, BMI, smoking initiation, alcohol consumption, and T2DM (**Figure 2**). Multivariable MR analysis revealed that after adjusting for smoking (OR = 2.68, 95% CI: 1.23–5.84, P = 1.30e−02), alcohol consumption (OR = 2.82, 95% CI: 1.39-5.71, P = 4.09e−03), BMI (OR = 3.74, 95% CI: 1.54–9.11, P = 3.64e−03), and T2DM (OR = 2.95, 95% CI: 1.19–7.31, P = 1.91e−02), short sleep duration remained causally related to the risk of ED. After adjusting for smoking (OR

Preprint

= 2.19, 95% CI: 1.42–3.39, P = 4.07e−04), alcohol consumption (OR = 2.14, 95% CI: 1.41-3.26, P = 3.60e−04), depression (OR = 1.76, 95% CI: 1.05–2.94, P = 3.21e−02), and T2DM (OR = 2.28, 95% CI: 1.34–3.90, P = 2.53e−03), frequent insomnia remained causally related to the risk of ED. Interestingly, after adjusting for depression for short sleep (OR = 2.05, 95% CI: 0.94–4.46, P = 7.03e−02) and after adjusting for BMI for frequent insomnia (OR = 1.66, 95% CI: 0.96–2.87, P = 7.19e−02), the causal relationship between these two sleep traits and ED risk was no longer present.

Discussion

To the best of our knowledge, this is the first study to comprehensively integrate the majority of sleep traits relevant to clinical practice and use multiple MR analysis to investigate the causal relationship between sleep traits and ED. Given the fact that ED patients often have poor sleep quality, it is currently inconclusive whether ED causes poor sleep quality or if poor sleep quality ultimately leads to ED. Our initial MR results demonstrated a causal relationship between morning chronotype and a lower risk of ED. Additionally, snoring was causally associated with a higher risk of ED. In contrast, our second set of MR results demonstrated that both short sleep duration and frequent insomnia were causally associated with a high risk of ED. Although the results of these two MR analyses were inconsistent, the causal relationships between sleep traits and ED were robust, as indicated by the sensitivity analysis. Furthermore, the association persisted in the multivariate analyses after adjusting for potential confounding factors. Meanwhile, our research found that there is no reverse causal relationship between sleep disorders and ED. Notably, after depression adjustment for short sleep and BMI adjustment for frequent insomnia, no causal association was

Preprint

found between these two sleep traits and ED risk.

Sleep is an essential internal activity for human health. Sleep disorders have been linked to various health problems, such as cardiovascular disease, obesity, mental health, and neurodegenerative diseases. Many of these conditions share common causes with ED [28]. Furthermore, medical interventions for sleep disorders, which often act through central nervous system pathways and include sedatives, may also impact ED [7]. Insomnia is a major form of sleep disorder characterized by difficulty in falling asleep, reduced sleep quality and duration, and impaired memory and concentration. Insomnia has been suggested as a potential risk factor for ED [7, 29]. Based on genetic data, our findings align with those of Yang et al. [30], indicating that insomnia increases the risk of ED. In contrast, other studies have failed to find a relationship between insomnia and ED [31, 32]. In their study, insomnia did not increase the risk of ED.

Snoring is another form of sleep disorder. A previous study provided genetic evidence that snoring, a feature of OSA, increases the risk of ED [33]. The relationship between OSA and ED has been extensively studied for several decades. However, there is conflicting evidence linking OSA with ED. Some studies have reported that OSA is not associated with ED [34, 35]. Another study reported a strong correlation between the severity of OSA and decreased sexual satisfaction, but no significant association with ED [8]. Continuous positive airway pressure (CPAP) and surgical treatments were demonstrated as effective therapies for OSA. It has been proved that CPAP therapy significantly improves erectile function of OSA patients, and a combined treatment with sildenafil provides a cumulative effect [36]. In addition, a large and long-term cohort study which included 11,116 OSA patients has shown that surgical treatments for OSA could reduce the risk for developing ED by 21% [37]. In

Preprint

our research, we have not identified genetic evidence of a causal relationship between OSA and ED.

Short sleep is also a form of sleep disorder. In modern society, the primary causes of short sleep among the public include shift work schedules, staying up late or developing late-sleeping habits, and engaging in various nighttime activities that disrupt sleep. According to Katherine et al. [38], men who work shifts, particularly night shifts, exhibit lower erectile function. This could be attributed to inadequate sleep and disrupted circadian rhythm. However, most studies have focused on investigating OSA and insomnia-related sleep disorders. Short sleep, similar to other sleep disorders, is equally important for meeting the social value requirements for clinical research [39].

Clinical observational studies have found that the association between sleep disorders and ED is unclear, primarily because of the presence of confounding factors. However, further research is needed to determine whether sleep disorders are risk factors for ED or whether they are comorbid symptoms of ED. Furthermore, there may be interactions or coexistence between different types of sleep disorders, making the establishment of a clear relationship between a specific type of sleep disorder and ED challenging. Although the specific mechanism by which sleep disorders contribute to ED is not yet fully understood, the prevailing belief is that the hypothalamic-pituitary-gonadal axis may have a significant effect on this phenomenon. In a 10-year follow-up cohort study that included 3314 participants, sleep disorders were found to disrupt the circadian rhythm of cortisol secretion. Individuals with sleep disorders showed a sharper surge in morning cortisol levels and higher cortisol levels later in the day than the control group [40]. According to the findings of the largest male patient cohort study to date, men diagnosed with circadian rhythm dysfunction,

Preprint

insomnia, or sleep apnea had higher risks of testosterone deficiency and ED [41]. Similarly, in a recent study by Katherine et al. [38], individuals with shift work sleep disorders were found to have lower testosterone levels compared to matched controls. Notably, testosterone therapy could partly reverse the effects of shift work sleep disorders and improve erectile function. Overall, most studies suggest that sleep disorders are associated with lower testosterone levels, which play an important role in the male erectile process. However, it was also observed that hypoxia may develop from sleep disorders [42]. It has been demonstrated that hypoxia can induce oxidative stress damage and downregulate the NO/cGMP signaling in sleep-deprived rat models [43]. Besides, sleep disorders and ED share common risk factors, such as mental disorders, obesity, hypertension, diabetes, and metabolic syndrome. These conditions also contribute to the development of ED.

This study has several highlights. First, previous research has focused only on one or a few sleep traits. In our study, we included a wide range of sleep traits commonly observed in clinical practice. We used univariate and multivariate MR methods to explore the causal relationship between these sleep traits and ED. Second, the present MR analysis was conducted using separate summary-level data from a large-scale GWAS, which enhanced the confidence of the inference due to the significant sample size. Third, the reliability of the results was improved by using various MR techniques and conducting sensitivity analyses.

However, this study has some limitations. First, the conclusions of this study may only be applicable to Europeans since the original GWAS summary-level data used in the analysis were sourced from European populations. Second, there may be some overlap between different sleep traits or between sleep traits and ED, which could result in overfitting and undermining causal inference. Finally, the diagnosis of sleep

Preprint

traits and ED was largely based on questionnaires, which may have introduced subjectivity. Moreover, the pharmacological treatment of sleep disorders may have a negative impact on erectile function, thereby influencing the accuracy of research findings. In the future, the use of multiple objective measures is advisable to diagnose sleep traits and ED to gain a better understanding of the relationship between sleep traits and ED outcomes.

Conclusion

This study strengthens the evidence that genetically predicted snoring and insomnia are associated with an increased risk of developing ED. Additionally, the study highlights the causal relationship between ED and short sleep duration, as well as chronotype. Employing more advanced analytical methods and utilizing updated GWAS data can enhance the accuracy and validity of our findings.

Preprint

References

1. Pang K, Pan D, Xu H, et al. Advances in physical diagnosis and treatment of male erectile dysfunction. Frontiers in physiology 2022; 13:1096741.

2. Mollaioli D, Ciocca G, Limoncin E, et al. Lifestyles and sexuality in men and women: the gender perspective in sexual medicine. Reproductive biology and endocrinology : RB&E 2020; 18:10.

3. Xiong Y, Zhang F, Zhang Y, et al. Insights into modifiable risk factors of erectile dysfunction, a wide-angled Mendelian Randomization study. Journal of advanced research 2024; 58: 149-161.

4. Ismail, A. M. A., & Hamed, D. E. Erectile dysfunction and metabolic syndrome components in obese men with psoriasis: response to a 12-week randomized controlled lifestyle modification program (exercise with diet restriction). Irish Journal Of Medical Science 2024; 193(1): 523-529.

5. Ismail, A. M. A. Post-COVID changes of semen parameters: a new era for physical activity that needs investigation. Андрология и генитальная хирургия 2023; 24(2): 126-129.

6. Ismail, A. M. A., El Gressy, N. S. S. A., Hegazy, M. D., Elfahl, A. M. A. H., & Ahmed, O. S. M. Randomized controlled effect of treadmill walking exercise on liver enzymes, psychological burden, and erectile dysfunction in men with hepatitis C. Gastroenterology Review/Przegląd Gastroenterologiczny 2023; 18(1).

7. Belladelli F, Li S, Zhang CA, et al. The Association Between Insomnia, Insomnia Medications, and Erectile Dysfunction. European urology focus 2024; 10(1): 139-145.

8. Gu Y, Wu C, Qin F, Yuan J. Erectile Dysfunction and Obstructive Sleep Apnea: A Review. Frontiers in psychiatry 2022; 13:766639.

9. Schiavi RC, Mandeli J, Schreiner-Engel P, Chambers A. Aging, sleep disorders,

Preprint

and male sexual function. Biological psychiatry 1991; 30:15-24.

10. Chen CM, Tsai MJ, Wei PJ, et al. Erectile Dysfunction in Patients with Sleep Apnea--A Nationwide Population-Based Study. PloS one 2015; 10:e0132510.

11. Chen KF, Liang SJ, Lin CL, Liao WC, Kao CH. Sleep disorders increase risk of subsequent erectile dysfunction in individuals without sleep apnea: a nationwide population-base cohort study. Sleep medicine 2016; 17:64-68.

12. Wu X, Zhang Y, Zhang W, et al. The Association Between Erectile Dysfunction and Sleep Parameters: Data from a Prospective, Controlled Cohort. The journal of sexual medicine 2022; 19:1387-1396.

13. Ference BA, Holmes MV, Smith GD. Using Mendelian Randomization to Improve the Design of Randomized Trials. Cold Spring Harbor perspectives in medicine 2021; 11.

14. Dashti HS, Jones SE, Wood AR, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nature communications 2019; 10:1100.

15. Lane JM, Jones SE, Dashti HS, et al. Biological and clinical insights from genetics of insomnia symptoms. Nature genetics 2019; 51:387-393.

16. Jansen PR, Watanabe K, Stringer S, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nature genetics 2019; 51:394-403.

17. Campos AI, García-Marín LM, Byrne EM, Martin NG, Cuéllar-Partida G, Rentería ME. Insights into the aetiology of snoring from observational and genetic investigations in the UK Biobank. Nature communications 2020; 11:817.

18. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nature genetics 2021; 53:1415-1424.

Preprint

19. Bovijn J, Jackson L, Censin J, et al. GWAS Identifies Risk Locus for Erectile Dysfunction and Implicates Hypothalamic Neurobiology and Diabetes in Etiology. American journal of human genetics 2019; 104:157-163.

20. Howard DM, Adams MJ, Clarke TK, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nature neuroscience 2019; 22:343-352.

21. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nature genetics 2018; 50:1505-1513.

22. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Human molecular genetics 2019; 28:166-174.

23. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nature genetics 2019; 51:237-244.

24. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. Statistics in medicine 2017; 36:1783-1802.

25. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. European journal of epidemiology 2017; 32:377-389.

26. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic epidemiology 2016; 40:304-314.

27. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. International

Preprint

journal of epidemiology 2017; 46:1985-1998.

28. Hale L, Troxel W, Buysse DJ. Sleep Health: An Opportunity for Public Health to Address Health Equity. Annual review of public health 2020; 41:81-99.

29. Cho JW, Duffy JF. Sleep, Sleep Disorders, and Sexual Dysfunction. The world journal of men's health 2019; 37:261-275.

30. Xiong, Y.; Zhang, F.-X.; Zhang, Y.-C.; et al. Genetically Predicted Insomnia Causally Increases the Risk of Erectile Dysfunction. Asian journal of andrology 2023; 25 (3): 421–425.

31. Martin S, Atlantis E, Wilson D, et al. Clinical and biopsychosocial determinants of sexual dysfunction in middle-aged and older Australian men. The journal of sexual medicine 2012; 9:2093-2103.

32. Seftel AD, Strohl KP, Loye TL, Bayard D, Kress J, Netzer NC. Erectile dysfunction and symptoms of sleep disorders. Sleep 2002; 25:643-647.

33. Xiong Y, Zhong X, Zhang F, et al. Genetic Evidence Supporting a Causal Role of Snoring in Erectile Dysfunction. Frontiers in endocrinology 2022; 13:896369.

34. Bozorgmehri S, Fink HA, Parimi N, et al. Association of Sleep Disordered Breathing with Erectile Dysfunction in Community Dwelling Older Men. The Journal of urology 2017; 197:776-782.

35. Hanak V, Jacobson DJ, McGree ME, et al. Snoring as a risk factor for sexual dysfunction in community men. The journal of sexual medicine 2008; 5:898-908.

36. Stilo, G.; Vicini, C.; Pollicina, I.; et al. Is Continuous Positive Airway Pressure a Valid Alternative to Sildenafil in Treating Sexual Dysfunction among OSA Patients? A Systematic Review and Meta-Analysis. Medicina (Kaunas) 2023; 59 (7): 1318.

37. Hwang, J.-H.; Ong, H.-L.; Chen, Y.-C. Surgical Treatments for Obstructive Sleep Apnea Decrease the Risk of Erectile Dysfunction: A Nationwide Cohort Study.

Preprint

Andrology 2022: 10 (3): 477–485.

38. Rodriguez KM, Kohn TP, Kohn JR, et al. Shift Work Sleep Disorder and Night Shift Work Significantly Impair Erectile Function. The journal of sexual medicine 2020; 17:1687-1693.

39. Zhang F, Xiong Y, Qin F, Yuan J. Short Sleep Duration and Erectile Dysfunction: A Review of the Literature. Nature and science of sleep 2022; 14:1945-1961.

40. Abell JG, Shipley MJ, Ferrie JE, Kivimäki M, Kumari M. Recurrent short sleep, chronic insomnia symptoms and salivary cortisol: A 10-year follow-up in the Whitehall II study. Psychoneuroendocrinology 2016; 68:91-99.

41. Agrawal, P.; Singh, S. M.; Able, C.; Kohn, T. P.; Herati, A. S. Sleep disorders are associated with testosterone deficiency and erectile dysfunction—a U.S. claims database analysis. International journal of impotence research 2024; 36(1): 78-82.

42. Sartor, F.; Ferrero-Bordera, B.; Haspel, J.; et al. Circadian Clock and Hypoxia. Circulation research 2024; 134 (6): 618–634.

43. Hamed, M. A.; Akhigbe, T. M.; Akhigbe, R. E.; et al. Glutamine Restores Testicular Glutathione-Dependent Antioxidant Defense and Upregulates NO/cGMP Signaling in Sleep Deprivation-Induced Reproductive Dysfunction in Rats. Biomedicine pharmacotherapy 2022; 148: 112765.

Preprint

Table 1: Detailed Information on Included Traits in This Study

Traits	Data source	Race	Cases	Controls	Sample size	nSNPs	PMID
Frequent Insomnia	UK Biobank	European	345,022	108,357	453,379	14,661,601	30804566
Short sleep duration	UK Biobank	European	106,192	305,742	446,118	14,661,601	30846698
Long sleep duration	UK Biobank	European	34,184	305,742	339,926	14,661,601	30846698
Sleep duration	UK Biobank	European	NA	NA	446,118	14,661,601	30846698
Morning chronotype	UK Biobank	European	252,287	150,908	403,195	11,977,376	30696823
Any Insomnia	UK Biobank	European	109,389	277,144	386,533	10,862,567	30804565
Sleep apnea syndrome	UK Biobank	European	13,818	463,035	476,853	24,183,940	34594039
Snoring	UK Biobank	European	152,302	256,015	408,317	10,707,662	32060260

Preprint

Erectile Dysfunction	UK Biobank	European	6,175	217,630	223,805	9,310,196	30583798
Depression	UK Biobank and Psychiatric Genomics Consortium	European	170,756	329,443	500,199	8,483,301	30718901
Body mass index	GIANT and UK Biobank	European	NA	NA	806,834	27,384,654	30239722
Smoking initiation	GSCAN consortium	European	NA	NA	341,427	11,983,806	30643251
alcohol consumption	GSCAN consortium	European	NA	NA	941,280	11,916,707	30643251
Type 2 diabetes mellitus	DIAGRAM consortium	European	80,832	817,298	898,130	23,465,132	30297969

SNP, single-nucleotide polymorphism; NA, not applicable.

Preprint

Table 2: The sensitivity analysis of MR analysis using IVs screened based on locus-wide significance (P < 1e-5).

Exposure	Cochran's Q test (IVW)	MR-Egger intercept test			MR-PRESSO global test		MR-steiger test
	P-value	Interpret	SE	*P*-value	RSSobs	*P*-value	*P*-value
Sleep duration	0.714	0.002	0.006	0.696	213.47	0.713	1.33E-263
Long sleep	0.962	0.004	0.010	0.718	55.32	0.962	2.79E-98
Short sleep	0.149	0.006	0.008	0.459	171.25	0.156	6.54E-136
Snoring	0.988	-0.012	0.007	0.098	157.58	0.988	1.29E-239
Sleep apnea syndrome	0.655	-0.013	0.011	0.239	43.41	0.676	1.36E-40
Morning person	0.154	-0.001	0.004	0.789	341.73	0.155	0
Any insomnia	0.892	0.006	0.008	0.466	90.12	0.900	4.61E-126
Frequent insomnia	0.100	-0.010	0.006	0.125	207.95	0.097	2.86E-179

MR, mendelian randomization; IVW, inverse variance weighted.

Preprint

Figure Legends

Figure 1 The causal effects of sleep traits on ED in univariable MR analysis using IVs screened based on the locus-wide significance.

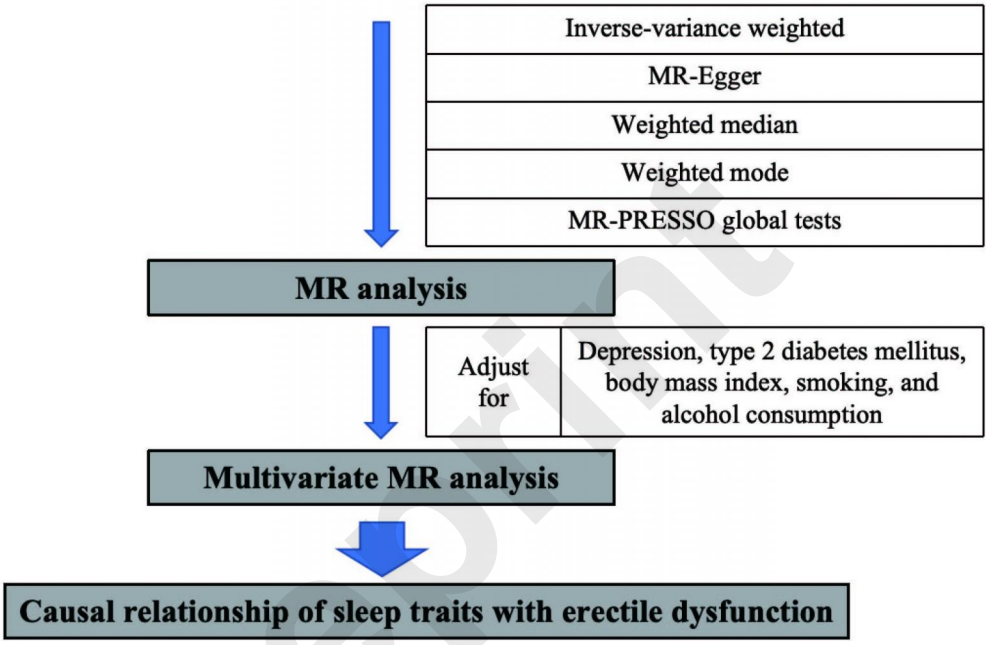
MR, mendelian randomization; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; ED, erectile dysfunction.

Figure 2 Multivariate MR results of the causal effects of short sleep and frequent insomnia on ED.

MR, mendelian randomization; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; ED, erectile dysfunction.

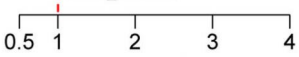
Preprint

Exposure	**Frequent Insomnia** 345,022 cases and 108,357 controls	**Any Insomnia** 109,389 cases and 277,144 controls
	Short sleep duration 106,192 cases and 305,742 controls	**Long sleep duration** 34,184 cases and 305,742 controls
	Sleep duration 446,118 individuals	**Morning chronotype** 252,287 cases and 150,908 controls
	Sleep apnea syndrome 13,818 cases and 463,035 controls	**Snoring** 152,302 cases and 256,015 controls
Outcome	**Erectile dysfunction**: 6,175 cases and 217,630 controls	



Preprint

Exposure	Method	nSNP	OR(95%CI)	Pvalue	P.adjust
Sleep duration	IVW	225	1.02(0.83−1.26)	8.46e−01	8.46e−01
Long sleep	IVW	75	3.34(0.92− 12.17)	6.74e−02	1.80e−01
Short sleep	IVW	152	3.02(1.59− 5.77)	7.82e−04	6.25e−03
Snoring	IVW	199	1.16(0.68− 1.97)	5.81e−01	7.07e−01
Sleep apnea syndrome	IVW	47	0.98(0.89−1.07)	6.18e−01	7.07e−01
Morning person	IVW	315	0.94(0.86−1.02)	1.26e−01	2.52e−01
Any insomnia	IVW	107	1.11(0.96−1.28)	1.74e−01	2.79e−01
Frequent insomnia	IVW	182	1.70(1.14−2.51)	8.57e−03	3.43e−02



Preprint

Exposure	nSNP	OR(95%CI)	Pvalue
Short sleep	187	2.68(1.23−5.84)	1.30e−02
Smoking initiation	187	0.90(0.61−1.32)	5.83e−01
Short sleep	791	3.74(1.54−9.11)	3.64e−03
Body mass index	795	0.95(0.85−1.06)	3.72e−01
Short sleep	241	2.82(1.39−5.71)	4.09e−03
Alcohol consumption	241	1.23(0.93−1.62)	1.40e−01
Short sleep	256	2.05(0.94−4.46)	7.03e−02
Depression	257	1.29(1.12−1.49)	4.04e−04
Short sleep	409	2.95(1.19−7.31)	1.91e−02
Type 2 diabetes mellitus	411	1.11(1.06−1.17)	6.00e−06
Frequent insomnia	196	2.19(1.42−3.39)	4.07e−04
Smoking initiation	195	0.79(0.51−1.22)	2.90e−01
Frequent insomnia	797	1.66(0.96−2.87)	7.19e−02
Body mass index	797	0.96(0.86−1.07)	4.70e−01
Frequent insomnia	203	2.14(1.41−3.26)	3.60e−04
Alcohol consumption	203	0.95(0.66−1.35)	7.62e−01
Frequent insomnia	249	1.76(1.05−2.94)	3.21e−02
Depression	249	1.21(1.03−1.44)	2.28e−02
Frequent insomnia	404	2.28(1.34−3.90)	2.53e−03
Type 2 diabetes mellitus	406	1.14(1.08−1.19)	1.04e−07

Preprint