International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Insomnia and Female Reproductive Diseases: A Cross-Sectional and Mendelian Randomization Study

Liyuan Fang[1,*], Yan Wang[1,*], Runxi Wang[1], Yuhang Fang[2], Yi Xie[2], Shuhan Yang[2], Suying Liu[1], Ying Zhang[1]

[1]Department of Oncology, Guang'anmen Hospital of the Chinese Academy of Traditional Chinese Medicine, Beijing, People's Republic of China; [2]Graduate School, Beijing University of Chinese Medicine, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying Zhang, Department of oncology, Guang'anmen Hospital of the Chinese Academy of Traditional Chinese Medicine, Beijing, 100053, People's Republic of China, Email zylzy501@163.com

Background: Insomnia is increasingly emerging as a significant concern in public health, with a longstanding emphasis on its relationship with overall well-being. Nevertheless, few research has been devoted to investigating the relationship between insomnia and female reproductive health.

Methods: In our study, we conducted a Mendelian randomization (MR) study to estimate the causal relationship between insomnia and female reproductive diseases. A total of 268 independent genetic variants associated with insomnia at the genome-wide significance level ($P < 5\times10^{-8}$) were used as instrumental variables. Summary-level data were obtained from the UK Biobank and Finn Gen study, including ovarian cysts, polycystic ovarian syndrome (PCOS), endometriosis, premature ovarian insufficiency (POI), ovarian cancer (OC), uterine fibroids, endometrial cancer (EC) and female infertility. We performed logistic regression to assess the associations between insomnia and the risk of OC and EC by using data from the National Health and Nutrition Examination Survey (NHANES) 2013–2014.

Results: Our research reveals that genetic liability to insomnia constitutes a risk factor for ovarian cysts (odds ratio [*OR*]: 1.44, 95% confidence interval [*CI*]: 1.21–1.72, $P< 0.05$), PCOS (*OR*: 1.67, 95% *CI*: 1.44–1.94, $P< 0.05$), and endometriosis (*OR*: 1.43, 95% *CI*: 1.16–1.76, $P< 0.05$). However, we found no statistically significant associations between insomnia and POI, OC, uterine fibroids, EC, or female infertility. Additionally, body mass index (BMI) was found to mediate about 10% of the effect of the insomnia on ovarian cysts and PCOS. Moreover, in cross-sectional study, insomnia was not associated with OC and EC.

Conclusion: Our study provides causal evidence that genetically predicted insomnia increases the risk of ovarian cysts, PCOS, and endometriosis. Accordingly, the potential significance of weight control and good sleep in keeping fit need to be emphasized.

Keywords: Mendelian randomization, insomnia, ovarian cysts, polycystic ovarian syndrome, endometriosis

Introduction

The ovaries and the uterus serve as essential reproductive and endocrine organs in female physiology, significantly contributing to procreation and keeping fit. However, in recent years, the female reproductive health has faced significant challenges. For instance, ovarian cysts affect approximately 7.8% of women of childbearing age,[1] while 6% of postmenopausal women have ovarian cysts detected during ultrasound examinations.[2] Conditions such as polycystic ovarian syndrome (PCOS), with a global prevalence of 4–20%,[3] and premature ovarian insufficiency (POI), affecting 3.5% of women,[4] highlight the widespread nature of these issues. In developed nations, Ovarian cancer (OC) and endometrial cancer (EC) are the most frequent malignancies affecting female reproductive health.[5,6] Primary symptoms of uterine fibroids and endometriosis encompass dysmenorrhea, menorrhagia, and fibroid compression, causing

Received: 6 November 2024
Accepted: 11 February 2025
Published: 18 February 2025

substantial psychological distress and physical discomfort for many women. Approximately 15% of the global female population faces infertility.[7] Furthermore, the increase in the prevalence of female reproductive diseases, particularly among younger individuals, adds significant burdens to society and families. Previous research has identified numerous risk factors for female reproductive disease, including obesity,[8] type 2 diabetes,[9] depression,[10] alcohol consumption,[11] and high-fat diets.[12] There is a growing awareness of the critical role of lifestyle interventions in disease control and prevention.[13] However, except for the above traditional risk factors, novel factors are scarcely studied, such as insomnia.

Sleep is a fundamental physiological need, playing a critical role in immune system function, metabolic processes, and tissue repair. In addition to its physiological importance, sleep also influences emotional well-being, cognition, and overall health. In the modern era, work demands, educational pressures, and daily stressors have contributed to a global increase in sleep disorders. Insomnia, a condition characterized by difficulties in initiating or maintaining sleep, affects approximately 30% of adults.[14] Notably, studies estimate that 38–59% of insomnia cases may have genetic underpinnings.[15]

Recent years have witnessed a wealth of research highlighting insomnia as an independent risk factor for various conditions, including hypertension,[16] depression,[17] viral infections[18] and neurodegenerative diseases.[19] Notably, modern females exhibit a higher prevalence of insomnia than males,[20] yet its impact on the ovaries and uterus remains a subject of mystery.

Mendelian randomization (MR) is an epidemiological methodology that strengthens causal inference by employing genetic variation as an instrumental variable for exposure.[21] This approach overcomes confounding and reverse causality effects inherent in cross-sectional, case-control, and cohort studies, ensuring the utmost reliability of research outcomes to the greatest extent possible. In this study, we used the MR approach to comprehensively assess the causal association between insomnia and eight female reproductive diseases, offering additional guidance for improving women's health.

Materials and Methods

Study Overview

The study design overview was shown in Figure 1. This study was based on summary-level data on measures of insomnia and from ovarian cysts, PCOS, endometriosis, POI, OC, uterine fibroids, EC and female infertility published genome-wide association studies (Figure 1A). In mediation analysis, the total effect was decomposed into direct effect and indirect effect (Figure 1B). Figure 1C shows flowchart identifying process of NHANES 2013–2014 participant inclusion and exclusion.

Source of Result Data

Genetic associations with female reproductive diseases were obtained from the UK Biobank[22] and the Finn Gen study.[23] We obtained genetic associations for ovarian cysts, PCOS, POI, endometriosis and female infertility from the Finn Gen research. There cases were defined by codes of International Classification of Diseases (8th, 9th and 10th revisions) with information from nationwide registries (Table S1). We utilized the R9 data release for the Finn Gen study, which became available in December 2022. Genetic associations for OC, EC and uterine fibroids were acquired from the UK Biobank. Similarly, cases were diagnosed by using codes of International Classification of Diseases (9th and 10th revisions) and self-reported information verified by interview with a nurse from national registries (Table S2). The details of the result have been described in previous studies (Table S3).

Genetic Instrument Selection

We identified single nucleotide polymorphisms (SNPs) associated with insomnia at a genome-wide significance level of $P < 5\times10^{-8}$. These SNPs were extracted from a genome-wide meta-analysis involving 2,365,010 individuals of European ancestry from the UK Biobank and 23andMe datasets.[24] Linkage disequilibrium (LD) among selected SNPs was estimated using the 1000 Genomes European reference panel. SNPs with LD ($r^2 > 0.01$) were excluded,[25] retaining the SNP with the smallest P value in the genetic association with insomnia. After clumping, 268 SNPs were selected as instrumental variables (Table S4).

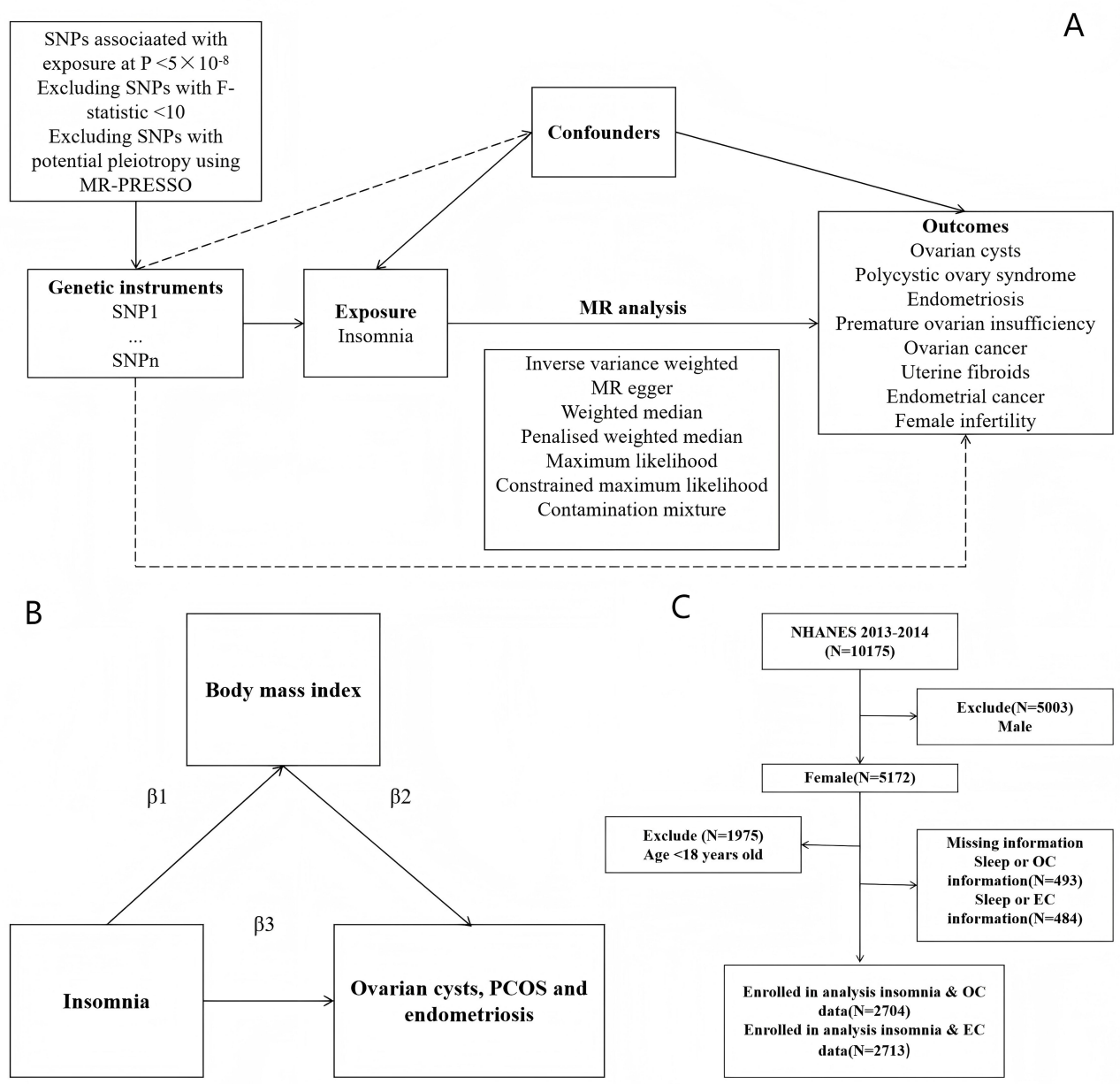

Figure 1 Study Design and Analytical Framework. (**A**), MR Analysis Framework. (**B**), Mediation Analysis Framework.β1: causal effects of insomnia on BMI, β2: causal effects of BMI on outcomes, β3: total causal effects of insomnia on outcome. (**C**), NHANES Data Selection Flowchart.

Mendelian Randomization Analysis

In the process of harmonization, we eliminated SNPs demonstrating palindromic sequences such as A/T or G/C alleles. Additionally, Steiger filtering was conducted to ensure the directional correlation between insomnia and female reproductive health. To address instrumental variable bias, our focus was specifically on individuals with an F-statistic exceeding 10 (F-statistic = $(\beta/SE)^2$). In our analysis, we primarily employed the random effects multiplicative inverse variance-weighted method.[26] Sensitivity analyses, including the weighted median,[27] penalized weighted median,[28] maximum likelihood,[28] constrained maximum likelihood,[29] contamination mixture,[30] MR-Egger,[31] and MR-PRESSO[32] were carried out to validate result consistency and detect potential horizontal pleiotropy. Assessing heterogeneity among SNP estimates for a single association was done through Cochran's Q value. Furthermore, we utilized the MR-Egger intercept test to investigate the presence of horizontal pleiotropy, while MR-PRESSO analysis was employed to identify

any potential outliers. Lastly, leave-one-out analysis was performed to assess the impact of specific SNPs on significant findings.

Two-Step MR and Mediation Analysis

In mediation analysis, the univariable MR method is employed to estimate the total effect of an exposure on the outcome. To explore whether an intermediary factor functions as a mediator between the exposure and outcome, a two-step MR approach was utilized.[33] Initially, the causal impact of insomnia on potential mediators was assessed. Subsequently, SNPs associated with potential mediating risk factors were utilized to evaluate their causal influence on conditions such as ovarian cysts, PCOS, and endometriosis. Body mass index (BMI) was considered a potential mediator in this context. The indirect influence of insomnia on ovarian cysts (or PCOS, endometriosis) through BMI was calculated by multiplying the effect of insomnia on BMI by the effect of BMI on ovarian cysts (or PCOS, endometriosis). It is important to highlight that in MR mediation analysis, the mediator must be a continuous variable to ensure the unbiased estimation of mediating effects.[34]

Cross-Sectional Study

The study included participants from the NHANES 2013–2014. Participants in this study were interviewed about demographics, socioeconomic, dietary habits, and health. OC and EC were collected by self-reports. Insomnia is defined as the self-reporting of sleep disturbances by participants, or the diagnosis of sleep disorders by doctor.

Statistical Analysis

All analyses were conducted with the "Two Sample MR" package (version 0.5.6), "MR-PRESSO" package (version 1.0.). and Mendelian Randomization (version 0.9.0) in R software (version 4.2.0). In descriptive statistics, continuous variables are expressed as means and standard deviations or medians and interquartile ranges, and categorical variables as proportions and percentages of the total. This research constructed logistic regression models to evaluate the associations of insomnia with OC and EC risk. Two Logistic regression models were constructed to assess the relationship. Model 1 was not adjusted. Model 2 was adjusted for age. It was considered statistically significant at $P < 0.05$ for all analyses, which were two-sided.

Results

MR Analysis

After selection, we identified 173, 191, 203, 189, 186, 213, 166 and 184 SNPs as genetic instruments for ovarian cysts, PCOS, POI, OC, EC, uterine fibroids, endometriosis and female infertility, respectively. Genetic liability to insomnia was associated with an increased risk of ovarian cysts (odds ratio [*OR*]: 1.37, 95% confidence interval [*CI*]: 1.17–1.60, *P*< 0.05), PCOS (*OR*: 1.51, 95% *CI*: 1.32–1.73, *P*< 0.05) and endometriosis (*OR*: 1.23, 95% *CI*: 1.02–1.48, *P*< 0.05) (Figure 2). Genetic liability to insomnia was not associated with POI (*OR*: 0.91, 95% *CI*: 0.34–2.42, *P*=0.85), OC (*OR*: 0.99, 95% *CI*: 0.99–1.01, *P*=0.87), uterine fibroids (*OR*: 1, 95% *CI*: 0.99–1.01, *P*=0.16), EC (*OR*: 1.04, 95% *CI*: 0.84–1.30, *P*=0.93) and female infertility (*OR*: 1.16, 95% *CI*: 0.97–1.40, *P*=0.28). The associations remained consistent but with wider CIs in the sensitivity analyses (Table S5).

Cochran's Q and MR-Egger intercept tests were performed to evaluate the robustness of these causal estimates. We observed no heterogeneity across SNPs' estimates in all analyses. We observed no indication of horizontal pleiotropy in MR-Egger intercept test. And pleiotropy tests using MR-PRESSO did not denote any pleiotropic SNPs, suggesting no bias in the results (Table S6).

Mediation MR Analysis

The two-step MR was employed to perform mediation MR analysis. We aimed to investigate whether the causal relationship between insomnia and female reproductive diseases could be mediated by BMI. Moreover, we found evidence that genetic liability to insomnia led to higher BMI (IVM: *OR*=1.30, 95% *CI*: 1.20–1.40, *P*< 0.05). Interestingly, our findings indicated that BMI played a role in the causal effect of insomnia on both PCOS (IVM: *OR*=1.22, 95% *CI*: 1.15–1.30, *P*< 0.05) and

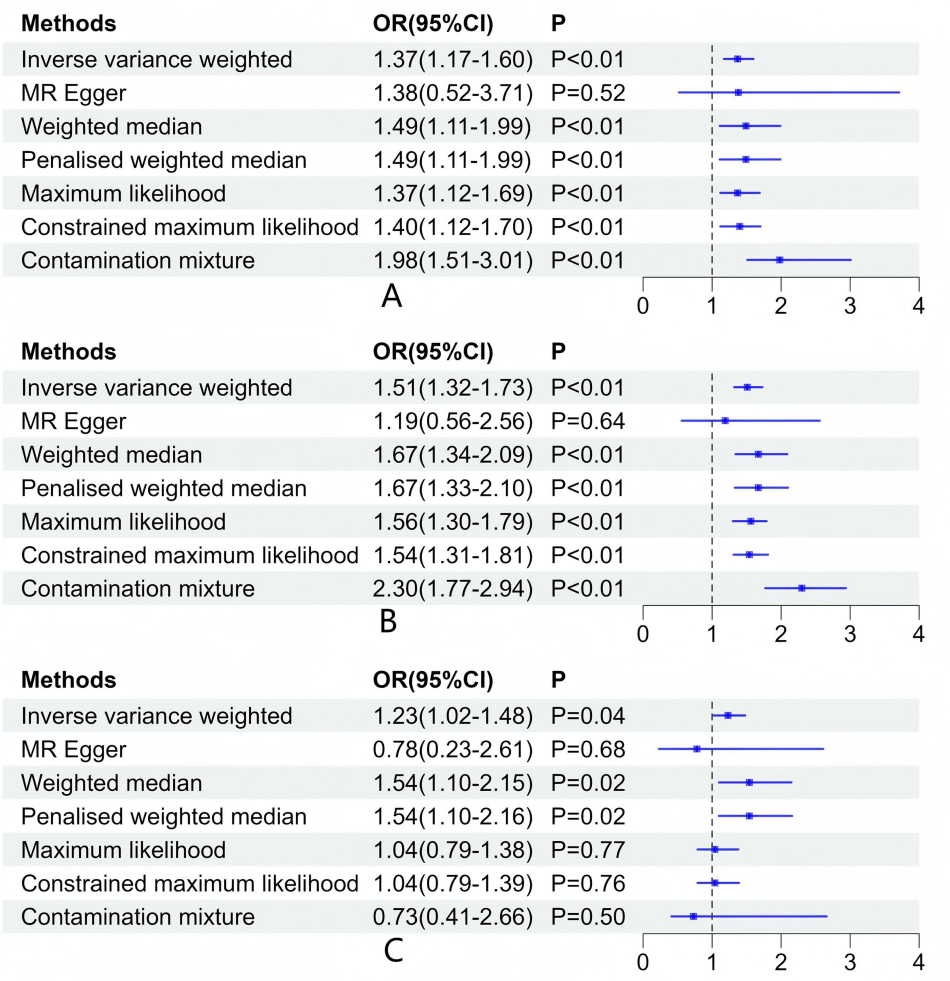

Figure 2 The forest plots. (**A**), Association of genetic liability to insomnia with risk of ovarian cysts, (**B**), Association of genetic liability to insomnia with risk of PCOS, (**C**), Association of genetic liability to insomnia with risk of endometriosis.

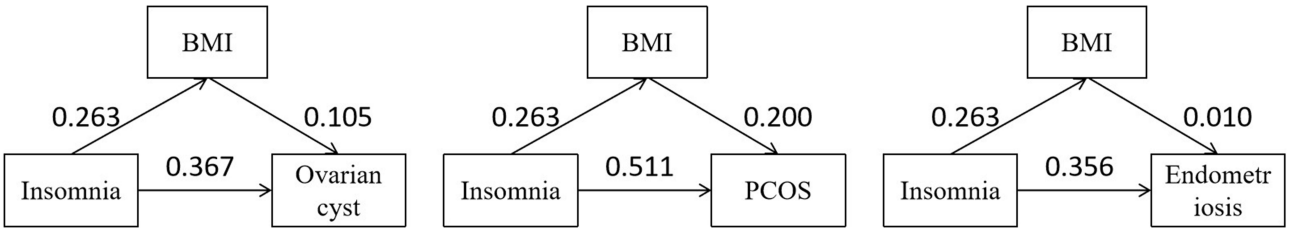

Figure 3 Mediation MR analysis outcomes.

ovarian cyst (IVM: *OR*=1.11, 95% *CI*: 1.04–1.19, *P*< 0.05). As shown in Figure 3, the mediation analysis revealed that BMI plays a significant role (10% mediation effect) in the causal pathway from insomnia to PCOS. And BMI mediate 8% effect of insomnia on ovarian cyst. BMI has little mediating effect between insomnia and endometriosis.

Characteristics of Study Participants at the Baseline

Demographic and clinical data about the study participants were displayed in Table S7, which were based on the diagnosis of OC and EC. There were five OC patients and fourteen EC patients. Patients with cancer were not statistically significant in age or insomnia compared with those without cancer.

https://doi.org/10.2147/IJWH.S498231

Associations of Insomnia With OC and EC

Followed by a correlation analysis between insomnia and OC/EC risk using progressively adjusted multivariate regression, the people without insomnia as a control. Insomnia was not associated with OC (*OR*=2.9, 95% *CI*: 0.47–17.71, *P*= 0.24) and EC (*OR*=1.49, 95% *CI*: 0.51–4.37, *P*= 0.46) after adjusting for age, similar in direction to the MR estimates (Table S8).

Discussion

To the best of our knowledge, this is the first large-scale two sample MR study utilizing data from the UK Biobank and Finn Gen databases to explore the relationship between genetically proxied insomnia and the risk of eight prevalent female reproductive diseases. Our research has revealed a noteworthy positive association between genetic liability to insomnia and the risk of ovarian cysts, PCOS, and endometriosis. In Mediation analysis, BMI was found to mediate about 10% of the effect of the insomnia on PCOS. In contrast, we found no substantial evidence to suggest a correlation between genetic liability to insomnia and the risk of POI, OC, uterine fibroids, EC, or female infertility. Insomnia was not link to elevated risk for OC and EC in observational study. The correlation existed persistently after full adjustment for confounders such as age.

Insomnia has emerged as a significant factor affecting both the quality of life and the physical well-being of individuals in the context of rapid socio-economic development. Extensive research efforts, including epidemiological and clinical studies, have been conducted to explore the complex relationship between insomnia and cancer risk in recent decades. A meta-analysis of fifteen prospective studies has revealed no correlation between sleep duration and the risk of breast cancer.[34] These associations were further strengthened in the MR study.[35] The two prospective studies demonstrated an increased risk of lung cancer and liver cancer in individuals with insomnia or shorter sleep durations when compared to those without insomnia.[36,37] Similar results have been reported for genetic liability to insomnia as a potential risk factor for other cancers.[38,39] Of note, researchers advocate for the maintenance of adequate nocturnal sleep to mitigate the occurrence of neoplasms. Furthermore, the interaction between sleep disturbances and non-neoplastic ailments plays a pivotal role in the clinical domain. A comprehensive meta-analysis of twenty studies has identified insomnia as a risk factor for type 2 diabetes.[40] What's worse, as sleep duration diminishes, the trajectory toward transitioning from prediabetes to full-fledged type 2 diabetes accelerates. Previous systematic reviews have similarly underscored the connection between insomnia and multimorbidity,[41] including cardiovascular diseases, obesity, and metabolic syndrome. Subsequent MR studies further strengthen this association.[42–44] Our study first conducts an MR study to estimate the complex relationship between insomnia and female reproductive health. Research findings unveil insomnia as a contributory risk factor for ovarian cysts, PCOS, and endometriosis.

Some underlying mechanisms in support of insomnia and the increased risk to female reproductive health have been proposed. First, estrogen, predominantly synthesized by the ovaries and meticulously governed by the hypothalamus-pituitary-gonadal axis, is pivotal in female overall well-being. An observational study has elucidated that premenopausal women with bad sleep quality manifest elevated levels of estradiol or testosterone within their physiological milieu.[45] This intricate network of connections is closely associated with an elevated risk of ovarian cysts, attributed to heightened estrogen levels. Moreover, persistent chronic inflammation is a widely recognized risk factor. A systematic meta-analysis of longitudinal studies delving into the intersection of sleep and inflammation discerns a clear correlation between sleep disturbances and heightened systemic inflammatory markers.[46] The adverse effects of poor sleep quality extend to an increased susceptibility to chronic conditions, including obesity, diabetes, and hypertension.[41] These chronic conditions stimulate the release of inflammatory mediators, ultimately leading to the development of a chronic inflammatory environment. Additionally, as we all know, that is a substantial influence wielded by vaginal microbiota over the female reproductive system. Disruptions in this intricate microbial ecosystem imperil the health of the female reproductive system. It is noteworthy that insomnia symptoms accelerate the aging process in women, precipitating dysbiosis, marked by a pronounced diminishment of lactobacilli.[47] What's worse, the absence of lactobacilli emerges as a critical factor contributing to the increased risk of endometriosis.[48] Considering these findings, future research endeavors should research deeper into exploring the mediating role of vaginal microbiota in elucidating the connection between insomnia

and female health. Such investigations hold profound implications for the advancement of clinical strategies in this domain.

Our findings may have potential public health and clinical practice consequences. Given the adverse implications of insomnia on ovarian cysts, PCOS, and endometriosis, the optimization of sleep patterns assumes paramount importance within the realm of female reproductive health. Strategies to enhance sleep quality include reducing pre-sleep smartphone usage, adherence to a consistent sleep schedule, regular physical activity, and so on. Moreover, dietary adjustments play an essential role in daily life, involving the reduction of high-fat and carbohydrate intake while augmenting protein and dietary fiber consumption. Lactobacilli emerge as crucial contributors to female health, such as Lactobacillus crispatus and Lactobacillus gasseri, demonstrating heightened viability in pasteurized milk stored at 4°C. The sustained consumption of milk fortified with lactobacilli not only fosters improved sleep quality but also exerts a beneficial influence on the vaginal microbiota.[49,50] When confronted with sleep disturbances, it is advisable to not only proactively implement the measures mentioned above but also consult with qualified medical professionals and employ appropriate interventions to safeguard their health.

There are several strengths in our research. First, our study conducts an MR study to examine the causal relationship between genetic liability to insomnia and female reproductive diseases, mitigating the interference of confounding factors. To ensure the robustness of our findings, a diverse array of statistical tests has been applied. Second, this study lies in the utilization of the latest and most comprehensive GWAS databases. We selected female insomnia-specific SNPs as instrumental variables, meticulously extracting them from the UK Biobank and Finn Gen databases. This approach provides a sturdy genetic foundation for our reported outcomes. Third, our careful selection of samples from disparate databases has been instrumental in alleviating the issue of sample overlap, thereby upholding the integrity of our results.

In addition, there are some limitations in this study. First, our study population exclusively comprises individuals of European descent, potentially constraining the generalizability of our findings to other demographic groups. Second, the limitations of Mendelian randomization should be carefully considered. These include the potential for distant or indirect correlations and the possibility of residual pleiotropy, which may bias causal interpretations. Third, our MR study was unable to access individual-level data, which posed a constraint on the depth of our analysis. Forth, the GWAS used self-reported insomnia rather than objective sleep assessment; thus, the validity of the information is not guaranteed. In addition, other common pathological factors, such as chronic inflammation and gut microbiota, may also play important roles and are worthy of further investigation.

Conclusion

In summary, our research provides compelling evidence supporting a significant causal relationship between insomnia and the risk of ovarian cysts, PCOS and endometriosis. These findings underscore the critical role of improving sleep quality and controlling weights in the preservation of female reproductive health. The mechanism behind these associations needs further study.

Data Sharing Statement

Analysis in this study was conducted using datasets that are publicly available. The data used in this study are freely available from the following sources: https://www.cdc.gov/nchs/nhanes/index.htm, https://gwas.mrcieu.ac.uk/ and. https://www.finngen.fi/en/access_results.

Ethics Statement

This study was approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (approval number: 2024-027-KY).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by Inheritance and Innovation Team of the National Administration of Traditional Chinese Medicine (grant number ZYYCXTD-C-202205) and Science and Technology Innovation Project of the China Academy of Chinese Medical Sciences (grant number CI2023C025YL).

Disclosure

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bottomley C, Bourne T. Diagnosis and management of ovarian cyst accidents. *Best Pract Res Clin Obstet Gynaecol*. 2009;23(5):711–724. doi:10.1016/j.bpobgyn.2009.02.001
2. Castillo G, Alcázar JL, Jurado M. Natural history of sonographically detected simple unilocular adnexal cysts in asymptomatic postmenopausal women. *Gynecol Oncol*. 2004;92(3):965–969. doi:10.1016/j.ygyno.2003.11.029
3. Nestler JE. Polycystic ovary syndrome. *N Engl J Med*. 2016;375: 1398.
4. M. L, Zhu Y, Wei J, et al. The global prevalence of premature ovarian insufficiency: a systematic review and meta-analysis. *Climacteric*. 2023;26:95–102. doi:10.1080/13697137.2022.2153033
5. Mazidimoradi A, Momenimovahed Z, Allahqoli L, et al. The global, regional and national epidemiology, incidence, mortality, and burden of ovarian cancer. *Health Sci Rep*. 2022;5(6):e936. doi:10.1002/hsr2.936
6. Zhai L, Yang X, Cheng Y, Wang J. Glutamine and amino acid metabolism as a prognostic signature and therapeutic target in endometrial cancer. *Cancer Med*. 2023;12(15):16337–16358. doi:10.1002/cam4.6256
7. Bala R, Singh V, Rajender S, Environment SK. Lifestyle, and Female Infertility. *Reprod Sci*. 2021;28:617–638. doi:10.1007/s43032-020-00279-3
8. Singh S, Pal N, Shubham S, et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. *J Clin Med*. 2023;12(4):1454. doi:10.3390/jcm12041454
9. Swerdlow AJ, Jones ME, Slater SD, et al. Cancer incidence and mortality in 23 000 patients with type 1 diabetes in the UK: long-term follow-up. *Int J Cancer*. 2023;153(3):512–523. doi:10.1002/ijc.34548
10. Geng S, Zhang X, Zhu X, et al. Psychological factors increase the risk of ovarian cancer. *J Obstet Gynaecol*. 2023;43(1):2187573. doi:10.1080/01443615.2023.2187573
11. K. L, Grundy A, Abrahamowicz M, et al. Alcohol intake and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2023;34:533–541. doi:10.1007/s10552-023-01681-3
12. Giles ED, Purcell SA, Olson J, et al. Trends in diet and cancer research: a bibliometric and visualization analysis. *Cancers*. 2023;15(15):3761. doi:10.3390/cancers15153761
13. Aurich S, Müller L, Kovacs P, Keller M. Implication of DNA methylation during lifestyle mediated weight loss. *Front Endocrinol*. 2023;14;1181002.
14. Roth T. Insomnia: definition, prevalence, etiology and consequences. *J Clin Sleep Med*. 2007;3(5 Suppl):S7–S10. doi:10.5664/jcsm.26929
15. Lind MJ, Aggen SH, Kirkpatrick RM, et al. A longitudinal twin study of insomnia symptoms in adults. *Sleep*. 2015;38(9):1423–1430. doi:10.5665/sleep.4982
16. Dai Y, Chen B, Chen L, et al. Insomnia with objective short sleep duration is associated with hypertension. *J Sleep Res*. 2023;32(4):e13833. doi:10.1111/jsr.13833
17. Soltani S, Noel M, Bernier E, Kopala-Sibley DC. Pain and insomnia as risk factors for first lifetime onsets of anxiety, depression, and suicidality in adolescence. *Pain*. 2023;164(8):1810–1819. doi:10.1097/j.pain.0000000000002879
18. Quan SF, Weaver MD, Czeisler MÉ, et al. Insomnia, poor sleep quality and sleep duration, and risk for COVID-19 infection and hospitalization. *Am J Med*. 2023;136(8):780–788. doi:10.1016/j.amjmed.2023.04.002
19. Lin W, Lin Y-K, Yang F-C, et al. Risk of neurodegenerative diseases in patients with sleep disorders: a nationwide population-based case-control study. *Sleep Med*. 2023;107:289–299. doi:10.1016/j.sleep.2023.05.014
20. Rumble ME, Okoyeh P, Benca RM. Sleep and women's mental health. *Psychiatr Clin North Am*. 2023;46(3):527–537. doi:10.1016/j.psc.2023.04.008
21. Lawlor DA, Harbord RM, Sterne JAC, et al. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133–1163. doi:10.1002/sim.3034
22. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779
23. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508–518. doi:10.1038/s41586-022-05473-8
24. Watanabe K, Jansen PR, Savage JE, et al. Genome-wide meta-analysis of insomnia prioritizes genes associated with metabolic and psychiatric pathways. *Nat Genet*. 2022;54(8):1125–1132. doi:10.1038/s41588-022-01124-w
25. Thorkildsen MS, Gustad LT, Mohus RM, et al. Association of genetically predicted insomnia with risk of sepsis: a mendelian randomization study. *JAMA Psychiatry*. 2023;80(10):1061–1065. doi:10.1001/jamapsychiatry.2023.2717

26. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Stat Med*. 2016;35(11):1880–1906. doi:10.1002/sim.6835
27. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
28. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985–1998. doi:10.1093/ije/dyx102
29. Xue H, Shen X, Pan W. Constrained maximum likelihood-based Mendelian randomization robust to both correlated and uncorrelated pleiotropic effects. *Am J Hum Genet*. 2021;108(7):1251–1269. doi:10.1016/j.ajhg.2021.05.014
30. Burgess S, Foley. CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. *Nat Commun*. 2020;11:376. doi:10.1038/s41467-019-14156-4
31. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. doi:10.1093/ije/dyv080
32. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50:693–698. doi:10.1038/s41588-018-0099-7
33. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. *Int J Epidemiol*. 2012;41(1):161–176. doi:10.1093/ije/dyr233
34. Carter AR, Sanderson E, Hammerton G, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. *Eur J Epidemiol*. 2021;36(5):465–478. doi:10.1007/s10654-021-00757-1
35. Aty. W, Heath AK, Tong TYN, et al. Sleep duration and breast cancer incidence: results from the Million Women Study and meta-analysis of published prospective studies. *Sleep*. 2021;44:zsaa166. doi:10.1093/sleep/zsaa166
36. Richmond RC, Anderson EL, Dashti HS, et al. Investigating causal relations between sleep traits and risk of breast cancer in women: Mendelian randomisation study. *BMJ*. 2019;365:l2327. doi:10.1136/bmj.l2327
37. Fang HF, Lee T-Y, Hui KC, et al. Association between sedative-hypnotics and subsequent cancer in patients with and without insomnia: a 14-year follow-up study in Taiwan. *J Cancer*. 2019;10:2288–2298. doi:10.7150/jca.30680
38. Cao Q, Zhang Q, Li XC, Ren CF, Qiang Y. Impact of sleep status on lung adenocarcinoma risk: a prospective cohort study. *Eur Rev Med Pharmacol Sci*. 2022;26:7641–7648. doi:10.26355/eurrev_202210_30040
39. Yang X, Wang J, Wang H. Association between sleep traits and primary liver cancer: a Mendelian randomization analysis. *Eur J Clin Invest*. 2023;53(8):14002. doi:10.1111/eci.14002
40. Huo Z, Ge F, Li C, et al. Genetically predicted insomnia and lung cancer risk: a Mendelian randomization study. *Sleep Med*. 2021;87:183–190. doi:10.1016/j.sleep.2021.06.044
41. Mostafa SA, Mena SC, Antza C, et al. Sleep behaviours and associated habits and the progression of pre-diabetes to type 2 diabetes mellitus in adults: a systematic review and meta-analysis. *Diab Vasc Dis Res*. 2022;19(3):14791641221088824. doi:10.1177/14791641221088824
42. Nistor P, Chang-Kit B, Nicholson K, Anderson KK, Stranges S. The relationship between sleep health and multimorbidity in community dwelling populations: systematic review and global perspectives. *Sleep Med*. 2023;109:270–284. doi:10.1016/j.sleep.2023.07.002
43. Hayes BL, Vabistsevits M, Martin RM, et al. Establishing causal relationships between sleep and adiposity traits using Mendelian randomization. *Obesity*. 2023;31(3):861–870. doi:10.1002/oby.23668
44. Liang YY, Chen J, Peng M, et al. Association between sleep duration and metabolic syndrome: linear and nonlinear Mendelian randomization analyses. *J Transl Med*. 2023;21(1):90. doi:10.1186/s12967-023-03920-2
45. Yang Y, Fan J, Shi X, et al. Causal associations between sleep traits and four cardiac diseases: a Mendelian randomization study. *ESC Heart Fail*. 2022;9:3160–3166. doi:10.1002/ehf2.14016
46. Nagata C, Wada K, Yamakawa M, et al. Sleep-related factors and circulating levels of sex hormones in premenopausal Japanese women. *Endocr J*. 2023;70(3):267–273. doi:10.1507/endocrj.EJ22-0337
47. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;80(1):40–52. doi:10.1016/j.biopsych.2015.05.014
48. Yoshikata R, Yamaguchi M, Mase Y, et al. Evaluation of the efficacy of Lactobacillus-containing feminine hygiene products on vaginal microbiome and genitourinary symptoms in pre- and postmenopausal women: a pilot randomized controlled trial. *PLoS One*. 2022;17(12):e0270242. doi:10.1371/journal.pone.0270242
49. Findeklee S, Urban L, Sima R-M, et al. The impact of the microbiological vaginal swab on the reproductive outcome in infertile women. *Life*. 2023;13(6):1251. doi:10.3390/life13061251
50. Chu A, Samman S, Galland B, Foster M. Daily consumption of Lactobacillus gasseri CP2305 improves quality of sleep in adults - A systematic literature review and meta-analysis. *Clin Nutr*. 2023;42:1314–1321. doi:10.1016/j.clnu.2023.06.019