Original Article

Insomnia in relation to 10 urological and reproductive conditions: a two-sample Mendelian randomization study

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Background: The causal association of insomnia with multiple urological and reproductive conditions still lacks clarity. Our aim was to assess this relationship by examining impact of insomnia on 10 urological and reproductive conditions using Mendelian randomization (MR) designs.

Methods: Summary statistics for insomnia and 10 urological and reproductive conditions were acquired from the UK Biobank, 23andMe, FinnGen, and genetic consortia. Inverse variance weighted approach was utilized as the main MR analysis. Sensitivity analyses were performed employing MR-PRESSO (Pleiotropy Residual Sum and Outlier), maximum likelihood, MR-Egger, and weighted median methods to examine the robustness of the estimates.

Results: Genetically determined insomnia showed an elevated risk of cystitis [odds ratio (OR) =1.81; 95% confidence interval (CI): 1.47–2.24; P<0.001], and prostatitis (OR =3.53; 95% CI: 1.73–7.18; P<0.001) after Bonferroni correction. Suggestive evidence of an association was found between insomnia and a heightened risk of prostate cancer (OR =1.30; 95% CI: 1.00–1.67; P=0.046), alongside a decreased risk of bladder cancer (OR =0.48; 95% CI: 0.26–0.90; P=0.02). No causal effects were observed for kidney cancer, kidney and ureter calculus, neurogenic bladder, benign prostatic hyperplasia (BPH), male infertility, or female infertility.

Conclusions: Findings support insomnia as a potential causal risk factor for cystitis and prostatitis. This highlights insomnia as an important target for reducing the risk of these diseases.

Keywords: Insomnia; urology; reproductive health; Mendelian randomization (MR); causal effect

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Introduction

Insomnia ranks as the second most prevalent mental disorder, affecting approximately 10% to 30% of the general population (1). Insomnia is defined by challenges in initiating or maintaining sleep, along with early morning awakenings, or experiencing a feeling of nonrestorative sleep (2). Increasing evidence from observational studies suggests that insomnia is correlated with various urological and reproductive conditions, including urologic cancers [such as prostate (3-5), kidney (4,5), and bladder cancer (4)], benign prostatic hyperplasia (BPH) (6), female infertility (7), urinary incontinence (8), kidney stones (9), and female sexual dysfunction (10). However, these associations derived from observational studies are susceptible to reverse causation bias and residual confounding. The causal associations between insomnia and these urological and

reproductive conditions remain unclear.

Mendelian randomization (MR) employs genetic variants, often single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to explore causal associations between exposures and outcomes. MR studies offer advantages over observational studies, as they are less susceptible to biases such as confounding and reverse causality (11). In the field of urological and reproductive medicine, two recent MR studies have shown the causal relationship between insomnia and lower total testosterone levels in men (12) as well as erectile dysfunction (13).

Nevertheless, the impact of insomnia on various other urological and reproductive health outcomes such as neurogenic bladder, cystitis, and prostatitis remains less well studied. Here, we conducted a sequence of two-sample MR investigations to examine the potential causal influence of insomnia on the susceptibility to 10 selected urological and reproductive conditions. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-444/rc) (11).

Methods

MR design and IVs selection

Genetic variants in MR must fulfill three core assumptions to serve as valid IVs: (I) a strong association with the exposure; (II) independence from confounders of the exposure-outcome relationship; and (III) influencing the outcome solely through the exposure.

Highlight box

Key findings

- Insomnia is genetically associated with an elevated risk of cystitis and prostatitis.

What is known and what is new?

- Insomnia is already recognized as a risk factor for certain health conditions, but its impact on urological and reproductive conditions remains unclear.
- This study identifies insomnia as a potential causal risk factor for cystitis and prostatitis, advancing our understanding of its broader health impacts.

What is the implication, and what should change now?

- Insomnia may be an important target for intervention strategies aiming at reducing the risk of urological diseases, specifically cystitis and prostatitis.
- Greater attention should be given to addressing sleep disorders in clinical practice to mitigate these risks.

Genetic variants linked to insomnia at the genome-wide significance level ($P<5\times10^{-8}$) were obtained from the latest meta-analysis of genome-wide association studies (GWASs) on insomnia. This meta-analysis included a combined sample size of 2,365,010 European individuals, comprising 386,988 participants from the UK Biobank (UKB) and 1,978,022 individuals from 23andMe (14). That study identified 791 independent lead SNPs ($r^2<0.1$) associated with insomnia, 114 lead SNPs for male-specific insomnia and 377 lead SNPs for female-specific insomnia. Insomnia assessment differed between cohorts: in the UKB, participants utilized a touchscreen device, while in 23andMe, an online survey was employed. In the UKB cohort, insomnia cases were participants who usually experienced difficulty falling asleep at night or awakening in the middle of the night. Conversely, in the 23andMe cohort, individuals who reported any phenotypic concept of poor sleep were considered insomnia cases.

We conducted linkage disequilibrium (LD) analysis using the 1,000 genomes European reference panel to identify independent SNPs. The LD threshold was set at $r^2<0.001$, and a clump window of >10,000 kb was applied. During data harmonization between exposure and outcome, ambiguous and palindromic SNPs were excluded. Additionally, SNPs associated with the exposure that could not be matched in the outcome GWAS data were also excluded. The proportion of variance in the phenotype explained by the genetic instruments was computed. To assess the strength of the genetic instruments, the F statistic was calculated, and SNPs with an F statistic below 10 were eliminated. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

GWAS data sources for 10 urological and reproductive outcomes

This study included 10 urological and reproductive outcomes, including kidney cancer, prostate cancer, bladder cancer, calculus of kidney and ureter, neurogenic bladder, cystitis, prostatitis, BPH, male infertility, and female infertility. We acquired summary-level genetic information for the outcomes from the FinnGen project, which collects genome and health data from Finnish health registries (15). Utilizing the R9 data release of FinnGen, GWAS analyses for each trait were adjusted for age, sex, 10 genetic principal components, and genotyping batch.

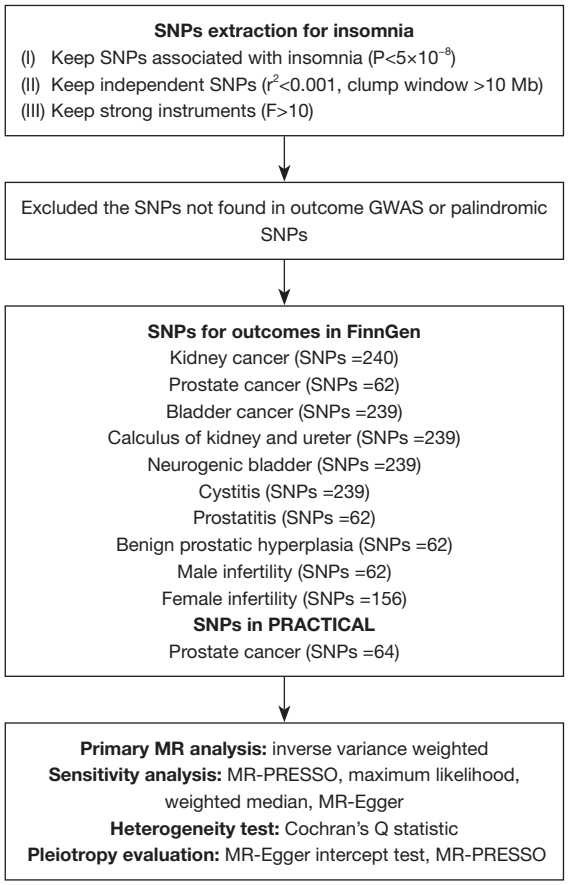

Figure 1 Overview of flow diagram in this MR study. SNPs, single nucleotide polymorphisms; GWAS, genome wide association study; PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome; MR, Mendelian randomization; PRESSO, Pleiotropy Residual Sum and Outlier.

Diseases were defined by the International Classification of Diseases (ICD) revisions 10, 9, and 8, procedure codes, and drug reimbursement codes. Additionally, summary-level genetic data on prostate cancer (comprising 61,106 controls and 79,148 cases) were sourced from the prostate cancer association group to investigate cancer associated alterations in the genome (PRACTICAL) consortium (16).

Statistical analysis

The main MR analyses were performed based on the inverse variance weighted (IVW) regression approach, which provides the most accurate estimates. This method assumes that all selected SNPs are valid instruments and balances potential pleiotropy. Post hoc power analyses for the primary IVW analyses were conducted using an online tool available at https://sb452.shinyapps.io/power/ (Table S1). Sensitivity analyses were also carried out employing MR-PRESSO (Pleiotropy Residual Sum and Outlier), maximum likelihood, MR-Egger, and weighted median methods to examine the robustness of the estimates. The heterogeneity among the IVs was assessed using Cochran's Q statistic and the global test from MR-PRESSO. To evaluate pleiotropy, we examined the intercept in the MR-Egger method. We used MR-PRESSO method to identify and adjust for potential outliers. Furthermore, MR estimates from various data sources were summarized using meta-analysis method. Cochrane Q test was employed for evaluating potential heterogeneity among the studies.

The results for MR analysis were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). As we included 10 urological and reproductive outcomes, the significance threshold was set at P<0.005 (0.05/10) after Bonferroni correction. Associations with P value ranging between 0.005 and 0.05 were classified as suggestive and warranted further validation. All statistical procedures were done in R software (version 4.2.0), utilizing R packages including TwoSampleMR (version 0.5.6), meta (version 6.1.0), and MRPRESSO (version 1.0).

Results

Basic characteristics

The study design, depicted in *Figure 1*, encompasses the criteria for both the inclusion and exclusion of candidate SNPs in each exposure-outcome pairing. In this MR study, data sources on GWAS datasets related to exposure and 10 outcomes are presented in Table S2. Detailed information regarding the genetic instruments utilized in the MR analysis can be found in the table available at https://cdn.amegroups.cn/static/public/10.21037tau-24-444-1.docx.

Causal associations of insomnia with urological and reproductive conditions

In terms of the four types of cancer, IVW MR analysis revealed suggestive associations between genetically determined insomnia and a higher risk of prostate cancer (OR =1.30; 95% CI: 1.00–1.67; P=0.046), while a reduced risk of bladder cancer was observed (OR =0.48; 95% CI: 0.26–0.90; P=0.02). However, genetically predicted

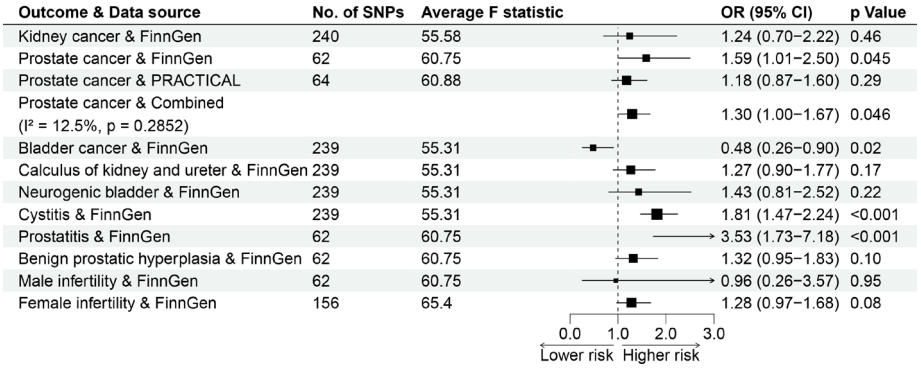

Figure 2 Forest plot of the causality between genetically predicted insomnia and 10 outcomes by inverse variance-weighted method. SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome.

insomnia did not show an association with kidney cancer (OR =1.24; 95% CI: 0.70–2.22; P=0.46) (*Figure 2*).

Regarding the five non-oncological diseases, the IVW MR analysis results revealed a correlation between genetically predicted insomnia and an elevated risk for cystitis (OR =1.81; 95% CI: 1.47–2.24; P<0.001) and prostatitis (OR =3.53; 95% CI: 1.73–7.18; P<0.001) after Bonferroni correction. However, no causal effect was observed for kidney and ureter calculus (OR =1.27; 95% CI: 0.90–1.77; P=0.17), neurogenic bladder (OR =1.43; 95% CI: 0.81–2.52; P=0.22), or BPH (OR =1.32; 95%CI: 0.95–1.83; P=0.10) (*Figure 2*).

For the remaining two reproductive health outcomes, no association was observed between genetically determined insomnia and female infertility (OR =1.28; 95% CI: 0.97–1.68; P=0.08). Similarly, there was no statistically significant association between genetically determined insomnia and male infertility (OR =0.96; 95% CI: 0.26–3.57; P=0.95) (*Figure 2*).

During the sensitivity analysis, the effect estimates for most outcomes were broadly consistent across the MR-PRESSO, maximum likelihood, and IVW approaches. Of note, the MR-Egger and weighted median approaches generally exhibited less precise estimates, reflected by wider CIs (Table S3).

Heterogeneity was observed in the analyses of prostate cancer as well as kidney and ureter calculus across SNPs, and possible pleiotropy was identified in the MR-Egger analysis of female infertility using the FinnGen data (Table S4). One outlier and two outliers were detected in the MR-PRESSO analysis of prostate cancer in PRACTICAL consortium and the analysis of calculus of kidney and ureter in FinnGen, respectively. After excluding the outliers, the results in the MR-PRESSO analysis remained largely unchanged (Table S4).

Discussion

This MR study, utilizing summary-level GWAS data, revealed a causal association between genetically determined insomnia and an elevated risk for cystitis and prostatitis. Additionally, there were suggestive associations of genetically determined insomnia with prostate cancer, and with a decreased risk for bladder cancer. However, no significant associations were detected for a range of other health outcomes, including kidney cancer, calculus of kidney and ureter, neurogenic bladder, BPH, female infertility, and male infertility.

Few studies have delved into the causal effects of insomnia on cystitis. An earlier observational study indicated that patients with interstitial cystitis/bladder pain syndrome(IC/BPS) faced an increased risk of developing insomnia (17). Among women with IC/BPS, poor sleep quality, short sleep duration, and disorder-specific sleep disturbances are prevalent (18). A nested case-control study discovered an elevated risk of subsequent IC/BPS among individuals with a history of sleep disorders (19). Sleep apnea represents a prevalent form of sleep disorder. A retrospective cohort analysis revealed that individuals diagnosed with obstructive sleep apnea (OSA) had a 3.71-fold increased likelihood of developing IC/BPS compared to those without OSA (20). Similarly, a recent case-control study reported an association between OSA and IC/BPS in women (21). Our study utilized MR design

to ascertain insomnia as a potential causal risk factor for cystitis. Despite these findings, the heterogeneous etiology of IC/BPS remains incompletely understood. Various potential pathologies have been mentioned in the literature, including chronic inflammation, epithelial denudation, sensitized or altered nervous system, and urothelial dysfunction (22).

Epidemiological studies investigating the link between sleep and prostatitis are limited. A cross-sectional study in Taiwan indicated a higher likelihood of chronic prostatitis in males diagnosed with OSA (23). While prior research has implicated neuroendocrine abnormalities, autoimmune imbalance, urinary microbial infection, and urinary reflux as predisposing factors for prostatitis (24), the mechanisms linking insomnia to prostatitis remain uncertain and need further investigation. A MR study revealed an association between insomnia and reduced total testosterone levels in men (12). Furthermore, evidence suggests that testosterone, especially dihydrotestosterone, may exert a protective effect by suppressing chronic inflammation in the prostate (25).

Studies examining the impact of insomnia on prostate cancer occurrence have produced inconsistent results. While three cohort studies consistently reported a higher risk of prostate cancer among individuals with insomnia (3-5), results from the Reduction by Dutasteride of Prostate Cancer Events trial suggested a positive association between insomnia and high-grade prostate cancer, with no significant link to overall or low-grade prostate cancer (26). Conversely, a prospective cohort research in Sweden, involving 14,041 men, found no indication of a link between sleep disturbance and prostate cancer risk (27). The disparities in outcomes observed across these observational investigations could be attributed to either reverse causation or confounding factors.

The precise biological mechanisms through which insomnia might increase cancer risk have not been fully elucidated. Nevertheless, Zhang *et al.* reported a significant association between insomnia and elevated inflammatory markers, such as interleukin-6, interleukin-1β, C-reactive protein, and tumor necrosis factor-alpha (28). It is widely acknowledged that inflammation is implicated in the process of carcinogenesis. Therefore, the observed association of insomnia with prostate cancer may be partially mediated by inflammation. In a prospective cohort study on bladder cancer, researchers reported that participants with insomnia had an elevated risk of developing bladder cancer (4). However, our MR study did not detect a similar effect. Several observational studies have investigated the link between insomnia and kidney cancer. Li *et al.* discovered a heightened risk of kidney cancer among 78,232 Chinese participants with insomnia (4). Moreover, a retrospective cohort study from Korea revealed an increased risk of kidney cancer in men with insomnia (5). Nevertheless, our investigation did not find substantial evidence to support a causal link between insomnia and kidney cancer. The differences in study populations and potential limitations in statistical power within our MR study may account for this discrepancy. Epidemiological studies on insomnia in relation to kidney and ureter calculi, BPH (6), neurogenic bladder, female infertility, and male infertility are limited, and results from our study based on MR suggested no causal associations.

There are several strengths in this study. First, our study represents the initial endeavor to explore the causal impacts of insomnia on urological and reproductive health outcomes using the MR approach, which offers heightened resilience against confounding factors and reverse causality. Second, we employed a robust set of genetic instruments derived from the latest large-scale GWAS to avoid weak instrumental bias and enhance credibility. Third, we ensured the absence of sample overlap between the exposure GWASs and FinnGen, thus minimizing the risk of type 1 errors. Fourth, the study primarily included individuals of European ancestry, thus population stratification bias was minimized.

This study is not without limitations. Firstly, insomnia was assessed through self-reported questionnaires, introducing subjectivity and potentially reducing precision in the evaluation. Insomnia is a heterogeneous phenotype consisting of multiple subdomains of symptoms. Of note, 23andMe insomnia phenotype was less accurate than the UKB insomnia phenotype, as it encompassed a broader range of sleep and medical conditions, including self-reported diagnoses of insomnia, sleep disturbance, narcolepsy, sleep apnea, and restless leg syndrome (14). This broader definition likely introduced additional heterogeneity into the phenotype classification, further limiting its specificity. Secondly, as the study participants were limited to European descent, the generalizability of the findings to the broader population may be limited. Thirdly, post-hoc power calculations indicated that the analyses for kidney cancer, bladder cancer, calculus of kidney and ureter, neurogenic bladder, BPH, male infertility, and female infertility were significantly underpowered, which could potentially distort results. Therefore, caution is warranted

in interpreting the associations.

Conclusions

The findings of MR analyses indicate that insomnia could be a plausible causal risk factor for cystitis and prostatitis. As sleep behaviours are modifiable, our findings also support the possibility that effective insomnia interventions might be beneficial to reduce the risk of these diseases. Subsequent research is required to confirm these findings among non-European populations to expand the generalizability and explore biological mechanisms.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-444/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-444/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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