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Genetically predicted effects of 10 sleep phenotypes on revision of knee arthroplasty: a mendelian randomization study

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Abstract

Background Accumulating evidence has suggested that sleep disturbances and disorders are common in patients who undergo knee arthroplasty. Revision surgery represents one of the most catastrophic outcomes of knee arthroplasty. However, it remains unclear whether sleep traits are the causes or consequences of knee arthroplasty revision. This study aimed to genetically examine the relationships between sleep traits and knee arthroplasty revision.

Methods To determine the causal relationship between sleep traits and knee arthroplasty revision, we employed two-sample Mendelian randomization (MR) using summary statistics from the largest publicly available genome-wide association studies (GWASs). The MR design uses genetic variants as instrumental variables to help separate causal relationships from non-causal associations. The main analyses included an inverse variance weighted (IVW) meta-analysis to obtain primary effect estimates. Sensitivity analyses involving the weighted median approach and MR-Egger regression were also conducted to check for potential pleiotropic biases. Numerous complementary sensitivity analyses were also performed to identify statistically significant causal correlations when there were horizontal pleiotropy and heterogeneity across variants. Finally, a reverse MR analysis was performed to evaluate the possibility of reverse causation.

Results In the absence of heterogeneity and horizontal pleiotropy, the IVW method revealed that genetically-predicted short sleep duration short sleep duration (average sleep duration of 24 h is 6 h or less) was positively correlated with the risk of knee arthroplasty revision (odds ratio = 1.03, 95% confidence interval = 1.01–1.05, and $P = 0.003$), while the association between genetically-predicted long sleep duration and knee arthroplasty was negative. The reverse MR analysis did not yield evidence supporting reverse causality relation between knee arthroplasty revision and sleep phenotypes.

Conclusion This research indicated that, of the 10 sleep phenotypes we analyzed, only sleep duration was causally associated with knee arthroplasty revision. These discoveries added to the understanding of the role of sleep traits

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in the etiology of knee arthroplasty revision, which might further expand our insights into the prevention of knee arthroplasty revision.

Highlights

- 1. Genetically-predicted short sleep duration increases risk of knee arthroplasty revision.
- 2. Mendelian randomization used to analyze sleep traits and knee revision relationship.
- 3. Sleep duration causally linked to lower risk of knee arthroplasty revision.
- 4. No evidence found for reverse causality between knee revision and sleep traits.
- 5. Study enhances understanding of sleep's role in knee arthroplasty outcomes.

Keywords Mendelian randomization, Knee arthroplasty revision, Sleep, Genome-wide association study, Causality

Introduction

Osteoarthritis (OA) is a degenerative joint disease that affects multiple joint tissues, including cartilage, subchondral bone, the infrapatellar fat pad, the meniscus, and the synovial membrane [1]. It is the most common joint disorder globally, with knee osteoarthritis being particularly prevalent, affecting approximately 16% of the global population [2]. The risk factors for OA can be broadly categorized into two groups: person-level factors (such as age, gender, obesity, genetics, and diet) and joint-level factors (including injury, malalignment, and abnormal joint loading) [3]. These factors interact in a complex manner to contribute to the onset and progression of the disease. Total knee arthroplasty (TKA) has emerged as the most efficacious and cost-effective intervention for managing advanced-stage knee arthritis. Despite the success of TKA, the escalating incidence of revision surgeries remains a formidable challenge, which not only threatens patients' health but also poses substantial pressure on healthcare systems [4]. Revision surgeries, necessitated by multiple factors, ranging from infection and aseptic loosening to periprosthetic fractures, subjecting patients to some significant risks including complications [5, 6]. Moreover, some of these surgeries occur under ambiguous circumstances—from minor technical glitches to psychological distress—highlighting a complicated interplay among various determinants of outcomes [7].

The intricate relationships among lifestyle, mental well-being, and physical health have been extensively acknowledged and might involve energy balance, metabolism [8], and patient engagement in rehabilitation and coping mechanisms [9]. These factors are crucial for promoting physical and functional recovery after TKA [10–12]. Sleep, a critical component of lifestyle and health, has drawn attention for its potential impact on the risk of revision total knee arthroplasty (rTKA) [13–15]. Evidence suggests that sleep duration and quality before and after joint replacement surgeries can significantly affect pain management, opioid use, and postoperative recovery [16–18]. For instance, improved sleep duration has been linked to lower postoperative pain levels [16]. Preoperative sleep quality was also strongly correlated with postoperative functionality, discomfort levels, and analgesic usage [18]. Nonetheless, the literature presents conflicting findings on the relationship between sleep and TKA outcomes. Some studies reported no direct association between preoperative sleep quality and postoperative pain [19, 20], while others, such as a study by Luo et al., found a significant influence of preoperative sleep characteristics on clinical outcome and postoperative length of hospital stay [18]. Sleep phenotypes have been proposed as potential risk factors for postoperative morbidity following primary joint arthroplasty. For instance, patients with sleep apnea have a higher rate of rTKA after undergoing TKA compared to those without sleep apnea [13, 21, 22],. Improved sleep quality and duration have been linked to better postoperative outcomes and higher patient satisfaction following TKA [23]. Enhanced sleep quality is also associated with lower pain levels and greater range of motion after surgery [24]. Moreover, preoperative sleep disorders have been identified as independent risk factors for chronic postsurgical pain following TKA [25]. Decreased functional capability can adversely affect sleep quality after TKA [26], and poor sleep quality has been correlated with worse patient-reported outcomes regarding function and pain [27]. Additionally, suboptimal sleep may impair immune function, increasing the risk of postoperative infection [28, 29]. Consequently, sleep disturbances may play a role in the need for rTKA.

Given these contradicting findings and the substantial impact of revision surgeries on patients' well-being and healthcare resources, this study aimed to conduct an in-depth investigation into this issue. We sought to clarify the causal relationship between sleep-related phenotypes and the likelihood of TKA patients undergoing revision surgery. By addressing this gap in the literature, our research endeavored to contribute to more comprehensive preoperative assessment and intervention strategies, with an attempt to mitigate the risk of revision surgeries and improve the outcomes of patients receiving TKA.

Mendelian randomization represents a methodological advancement capable of addressing the challenges of

unmeasured confounding and reverse causation inherent to traditional observational epidemiological studies [30]. This approach facilitates causal inference by employing genetic variants as proxies for modifiable risk factors or health outcomes [31]. Specifically, MR leverages genetic data, such as single nucleotide polymorphisms (SNPs) [32], which are associated with an exposure (e.g., sleep phenotype), and uses these as instrumental variables. This methodology allows for the assessment of the causal impact of the exposure on an outcome of interest (in this instance, revision total knee arthroplasty). One of the principal advantages of MR is its utilization of genetic variants that are randomly allocated at conception. This inherent randomness enables the simulation of a randomization process, thereby offering a quasiexperimental design that mitigates the biases associated with observational studies [33]. These genetic variants are not influenced by behavioral or environmental factors throughout the lifetime of an individual, thereby significantly reducing susceptibility to bias from reverse causation and the impact of transient fluctuations in exposure. Consequently, the effects observed in MR studies can be interpreted as reflecting lifetime exposure differences, enhancing the validity of the causal inferences drawn [34]. To our knowledge, no study prior to this study has elucidated the causal effect of sleep traits on revision after knee arthroplasty. In the present study, we conducted a Mendelian randomization analysis, drawing upon summary statistics from extensive genome-wide association studies (GWASs). Our objective was to investigate the causal relationship between sleep traits and the necessity for revision total knee arthroplasty. Furthermore, a sensitivity analysis was meticulously conducted, aiming to evaluate the influence of our hypotheses on the study findings and to verify the robustness and reliability of the results obtained.

Materials and methods

Data sources

Sleep-related phenotypes

By searching PubMed for published genome-wide association studies (GWASs), a total of 10 sleep-related traits were ascertained, including sleep duration, short sleep duration, long sleep duration [35], daytime napping [36], insomnia [37], chronotype [38], daytime sleepiness [39], snoring [40], sleep apnea [41], and trouble falling asleep [40]. The data sources for each sleep trait are summarized in Table 1. The genetic variant relationships for all the sleep phenotypes were evaluated in participants with European ancestry, and all GWAS data were adjusted for sex, age, and study-specific variables.

Revision of knee arthroplasty

The GWAS summary statistics of rTKA were obtained from the MRC-IEU consortium, which included 5,657 cases and 457,276 controls of European ancestry. Moreover, GWASs were adjusted for age, sex, and several principal components. A total of 9.85 million variants were retrieved.

Data availability

The data used in the MR analysis were publicly available and did not require specific ethical approval. The summary GWAS data of the sleep-related traits are available at The NHGRI-EBI GWAS Catalog (available at: https://www.ebi.ac.uk/gwas/home, accessed date: 1 February 2024) and The Sleep Disorder Knowledge Portal (SDKP, RRID: SCR_016611, available at: http://sleepdisordergenetics.org/, accessed date: 1 February 2024). The GWAS Catalog represents a comprehensive, publicly accessible resource that aggregates and curates all published genome-wide association studies (GWAS) and their associated findings. This catalog is the result of a collaborative effort between the National Human Genome Research Institute (NHGRI) and the European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI). Since the inception of the first GWAS on age-related macular degeneration in 2005, the catalog has consistently included all eligible studies, summarizing an extensive array of heterogeneous and unstructured data from the scientific literature into a coherent, meticulously curated, and quality-controlled repository [42]. The data contained within the catalog serve as a foundational resource for a wide range of researchers, including biologists, bioinformaticians, and clinical/translational scientists. This study provided a critical starting point for subsequent exploratory initiatives aimed at identifying causal genetic variants, elucidating the underlying mechanisms of diseases, and pinpointing potential targets for the development of novel therapeutic interventions. To be considered for inclusion within the GWAS Catalog, both studies and their reported associations are subject to rigorous selection criteria. Specifically, studies must be based on array technologies and analyze more than 100,000 single nucleotide polymorphisms across the genome. Moreover, SNP-trait associations are required to demonstrate statistical significance, with a P value threshold set at less than 1×10^{-5}. This stringent inclusion criterion ensures that the catalog remains a high-quality, reliable resource for the scientific community, facilitating advanced research and discovery in the field of genomics [43]. The Sleep Disorder Knowledge Portal constitutes an integral component of the Common Metabolic Diseases Knowledge Portal (CMDKP). The CMDKP consolidates and examines an extensive array of genetic association findings, epigenomic annotations,

Table 1 The sleep traits GWAS used for MR analyses

Traits	Phenotype definition (units)	Sample size (cases/controls for binary traits)	Number of instrumental variables	Cohort/Consortium	Covariate adjustment
Sleep duration [35]	Average duration of sleeping in 24 h, including naps (continuous variable, hours)	460,099	62	MRC-IEU	Age, sex, ten primary ancestry components, genotyping array, and genetic association matrix with a maximum of 10% missing data per SNP and 40% missing data per sample
Short sleep duration [35]	Average sleep duration of 24 h is 6 h or less vs. 7–8 h (binary variable of yes/no)	411,934 (106,192/305,742)	25	UKBB	Age, sex, ten primary ancestry components, genotyping array, and genetic association matrix with a maximum of 10% missing data per SNP and 40% missing data per sample
Long sleep duration [35]	Average sleep duration of 24 h is 9 h or more vs. 7–8 h (binary variable of yes/no)	339,926 (34,184/305,742)	5	UKBB	Age, sex, ten primary ancestry components, genotyping array, and genetic association matrix with a maximum of 10% missing data per SNP and 40% missing data per sample
Daytime napping [36]	Having a nap during the day (categorical variables categorized as never/rarely, sometimes, usually)	452,633 (255,746/172,897/23,990)	99	UKBB	Age, sex, ten primary ancestry components, genotyping array, and genetic association matrix with a maximum of 10% missing data per SNP and 40% missing data per sample
Insomnia [37]	Difficulty falling asleep at night or waking up in the middle of the night (binary variables categorized as "usually" vs. "never/rarely")	453,379 (129,270/108,357)	38	UKBB	Age, gender, the 10 main ancestry components, and a genotyping array
Chronotype [38]	Considering yourself as morning/evening person (ordered categorical variable of definitely a morning person, more a morning than an evening person, do not know, more an evening than morning person and definitely an evening person)	449,734	140	UKBB and 23andMe	Age, sex, study center and a derived variable representing genotyping release
Daytime sleepiness [39]	Unconsciously dozing off or falling asleep during the day (categorical variables categorized as never, sometimes, often and all the time)	452,071 (347,285/92,794/11,963/29)	37	UKBB	Age, sex, genotyping array, ten principal components of ancestry and genetic relatedness matrix
Snoring [40]	Creating noise while sleeping (binary variable of yes/no)	456,348 (151,836/255,230)	39	UKBB	Age, sex, genotyping array, 20 principal components of ancestry and genetic relatedness matrix
Sleep apnea [41]	Subjective symptoms, clinical examination and sleep registration applying AHI ≥ 5/hour or respiratory event index (REI) ≥ 5/hour (binary variable of yes/no)	218,998 (16,794/201,998)	3	FinnGen	Age, sex, genotyping array, ten principal components of ancestry and genetic relatedness matrix
Trouble falling asleep [40]	Taking more than 30 min to fall asleep (binary variables categorized as yes or no)	57,215 (43,474/13,741)	4	UKBB	Age, sex, genotyping array, ten principal components of ancestry and genetic relatedness matrix
Knee arthroplasty revision	Undertaking the revision surgery of knee arthroplasty (binary variables categorized as yes or no)	462,933 (5,657/457,276)	19 [#]	MRC-IEU	Age, sex, study center and a derived variable representing genotyping release

MR: Mendelian randomization; SNP: single nucleotide polymorphism; [#] We used a relaxed threshold ($P<5\times10^{-6}$) to select more SNP of rTKA in the reverse MR analysis.

and outputs from computational prediction methodologies. This comprehensive aggregation facilitates the provision of data, visualizations, and analytical tools within an open-access framework. The development and maintenance of the CMDKP are underpinned by funding from the Accelerating Medicines Partnership. A collaborative effort spearheads this initiative, comprising a dedicated team of scientists and software engineers affiliated

with the Broad Institute, the University of Michigan, and the University of Oxford. Furthermore, the project benefits from the contributions of numerous other partners spanning academic institutions, the industrial sector, and non-profit organizations globally. This collaborative approach ensures that the CMDKP population remains a pivotal resource for advancing the understanding of sleep disorders within the broader context of common metabolic diseases [35].

The summary statistics concerning the knee arthroplasty revision GWAS are available at the IEU Open GWAS (available at: https://gwas.mrcieu.ac.uk, accessed date: 1 February 2024). The IEU Open GWAS database represents a cutting-edge, open-source, open-access data infrastructure designed with scalability and high performance in mind and is hosted on a cloud-based platform. Its primary function is to import and disseminate comprehensive GWAS summary datasets along with their corresponding metadata to facilitate research within the scientific communities [44]. As of the current update, it houses approximately 126 billion genetic associations derived from 14,582 complete GWAS datasets. These datasets span a diverse array of human phenotypes and disease outcomes, encompassing a variety of populations. This expansive and meticulously curated collection serves as a valuable resource for researchers aiming to advance our understanding of genetic underpinnings across a broad spectrum of human conditions [45].

Selection of instrumental variables (IVs)

In MR analyses, valid instrumental variables are characterized by three key assumptions (Fig. 1): relevance, independence, and exclusion restriction. The relevance assumption states that instrumental variables are associated with the risk factor of interest. The independence assumption expounds that instrumental variables do not share any common causes with the outcome. Finally, the exclusion restriction assumption dictates that instrumental variables affect the outcome only indirectly through the risk factor and not directly through the outcome itself [46].

Mendelian Randomization (MR) uses genetic variants (SNPs) as proxies for modifiable risk factors to assess causal relationships between exposures (such as sleep

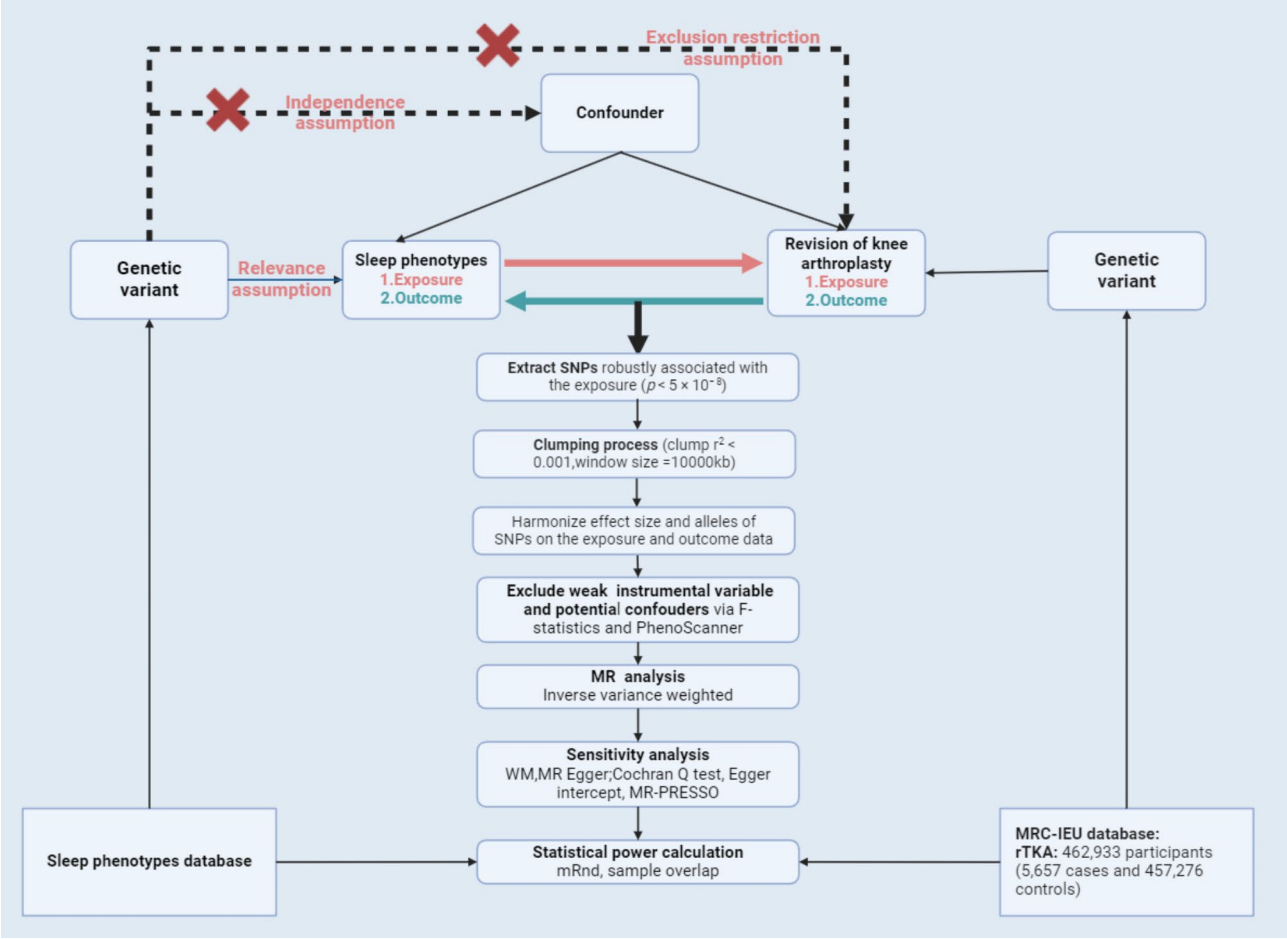

Fig. 1 Flowchart of the MR study design

traits) and outcomes (such as knee arthroplasty revision). We sourced genetic data from large GWAS databases for sleep traits and knee arthroplasty revision, selecting SNPs significantly associated with sleep traits ($P<5\times10^{-8}$) and ensuring independence through clumping ($R^2<0.001$). After aligning effect sizes and alleles across datasets, we excluded weak instruments and potential confounders using F-statistics and PhenoScanner. The primary MR analysis was conducted using the Inverse Variance Weighted (IVW) method, with additional sensitivity analyses (MR-Egger, weighted median, MR-PRESSO) to check for pleiotropy and other biases. Statistical power calculations were performed to ensure robustness. Our results indicated a causal relationship between sleep traits and knee arthroplasty revision, with short sleep duration increasing the risk and long sleep duration decreasing it, confirmed through rigorous sensitivity checks.

To select valid instrumental variables, we employed several quality control procedures. We began by identifying single nucleotide polymorphisms (SNPs) related to exposure at the genome-wide significance threshold ($P<5\times10^{-8}$ for sleep traits and $P<5\times10^{-6}$ for revision of knee arthroplasty) from the initial GWAS. Then, we applied the Plink clumping procedure with $R^2<0.001$ and a window size of 10,000 kb to ensure that the selected SNPs were independent and free from linkage disequilibrium (LD). To minimize weak instrument bias, we employed F-statistics > 10 for all exposures. We also eliminated palindromic SNPs to prevent distortion of strand orientation or allele coding. Finally, we addressed potential pleiotropy by removing SNPs via the MR pleiotropy residual sum and outlier (MR-PRESSO) method. The details are provided in the Supplementary Tables (Supplementary Information).

Statistical analysis

The inverse variance weighted (IVW) method was utilized for weighting the influence of each SNP on exposure and outcome data as the best-powered unbiased estimation of determining causality if there was no horizontal pleiotropy and if all IVs were valid [47]. When pleiotropy existed, the MR–Egger, weighted median, and weighted mode approaches were also used to obtain more reliable and robust estimates. If there was heterogeneity among the SNPs included in each analysis, random effects IVW was performed.

We utilized the PhenoScanner database (available at: http://www.phenoscanner.medschl.cam.ac.uk, accessed date: 1 February 2024) to explore potential associations of the chosen SNPs with confounding traits. After excluding these SNPs, we re-performed the analysis [48]. R^2 and F-statistics were calculated to explore weak IV bias using a previously reported method [49]. R^2 is the fraction of variation explained by IVs in exposure factors, and an F-statistic < 10 indicates that the weak IV bias will be abolished.

Sensitivity analyses

To evaluate the sensitivity of genetic causal effects, we conducted a series of sensitivity analyses by using MR-Egger regressions and weighted median methods. In addition, we estimated directional pleiotropy via the MR–Egger intercept and evaluated different genetic variants by adopting Cochran's Q statistic to assess heterogeneity among IVW estimates [50]. Furthermore, we employed MR-PRESSO to evaluate and adjust potential outlier SNPs [51]. The leave-one-out sensitivity method was employed to ascertain whether a particular genetic locus had an effect on random estimates. To further highlight the sensitivity of the findings, scatterplots, forest plots, and funnel plots were generated.

Statistical power and bias and type 1 error rate

The post statistical power was calculated using an online tool (available at: https://sb452.shinyapps.io/power, accessed date: 1 February 2024). We carried out the analyses of Bias and Type 1 Error Rate for Mendelian Randomization with Sample Overlap to evaluate the potential bias caused by sample overlap using a website-based tool (available at: https://sb452.shinyapps.io/overlap/, accessed date: 1 February 2024) [52].

We set the threshold for statistical significance at $P<0.005$ (Bonferroni corrected P-value correcting for 10 exposures and 1 outcome) [53, 54]. Additionally, a bidirectional MR test was carried out. A P value between 0.005 and 0.05 was considered to indicate evidence of a potential relationship. The "TwoSampleMR" and "MRPRESSO" packages in R, along with R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria), were used for all the statistical analyses.

Results

The complete MR analysis information is presented in the Supplementary Tables, including the characteristics of the selected SNPs for each sleep trait, the outcomes of the heterogeneity tests, and the results of the causal effect estimates.

Table S1 summarizes sleep-associated SNPs from GWAS. Table S2 compares causal effects of sleep phenotypes on knee revision. Table S3 assesses causal effects of knee revision on sleep phenotypes. Table S4 outlines SNPs relating to knee arthroplasty revision. Table S5 examines causal relationships between sleep factors and hip arthroplasty.

Causality between sleep traits and knee arthroplasty revision

As depicted in Fig. 2, there was compelling evidence of a causal relationship between sleep duration and rTKA according to the IVW method (odds ratio (OR)=0.99, 95% confidence interval (95%CI): 0.98–0.99, and P=0.00004) and weighted median method (OR=0.99, 95%CI: 0.98–0.99, and P=0.0007). For 62 instruments, MRPRESSO detected no potential outliers. In addition, a causal relationship was found between short sleep duration (average sleep duration of 24 h is 6 h or less) and knee arthroplasty revision according to the IVW method (OR=1.03, 95%CI=1.01–1.05, and P=0.003). For 22 IVs, there was no potential outlier according to

Exposure	Method	nSNPs	p.value	OR(95%CI)	Heterogeneity.Test.P	Pleiotropy.Test.P
Sleep duration	MR Egger	62	0.479980811	0.99(0.97 to 1.02)	0.08527944	0.7452146
	Weighted median	62	0.000706890	0.99(0.98 to 0.99)		
	Inverse variance weighted	62	0.000042100	0.99(0.98 to 0.99)	0.09800735	
	Simple mode	62	0.068542099	0.98(0.96 to 1.00)		
	Weighted mode	62	0.076136944	0.98(0.97 to 1.00)		
Short sleep duration	MR Egger	22	0.087243025	1.09(0.99 to 1.20)	0.09969971	0.2361214
	Weighted median	22	0.014626545	1.03(1.01 to 1.06)		
	Inverse variance weighted	22	0.003611901	1.03(1.01 to 1.05)	0.08155081	
	Simple mode	22	0.119017655	1.04(0.99 to 1.10)		
	Weighted mode	22	0.079372249	1.05(1.00 to 1.10)		
Long sleep duration	MR Egger	5	0.815573069	1.07(0.67 to 1.70)	0.09313587	0.6809551
	Weighted median	5	0.046856734	0.94(0.88 to 1.00)		
	Inverse variance weighted	5	0.159450224	0.95(0.89 to 1.02)	0.15205323	
	Simple mode	5	0.212017359	0.92(0.83 to 1.02)		
	Weighted mode	5	0.152865354	0.92(0.84 to 1.00)		
Insomnia	MR Egger	36	0.106360083	1.05(0.99 to 1.12)	0.5038357	0.1381055
	Weighted median	36	0.102613730	1.01(1.00 to 1.02)		
	Inverse variance weighted	36	0.276225102	1.00(1.00 to 1.01)	0.4416906	
	Simple mode	36	0.186605350	1.02(0.99 to 1.05)		
	Weighted mode	36	0.192774804	1.02(0.99 to 1.04)		
Daytime napping	MR Egger	96	0.750842572	1.00(0.98 to 1.02)	0.3006402	0.9137558
	Weighted median	96	0.956461406	1.00(0.99 to 1.01)		
	Inverse variance weighted	96	0.447343291	1.00(1.00 to 1.01)	0.325903	
	Simple mode	96	0.774075821	1.00(0.98 to 1.02)		
	Weighted mode	96	0.744999809	1.00(0.98 to 1.01)		
Daytime sleepiness	MR Egger	36	0.520227634	1.02(0.96 to 1.08)	0.04784131	0.5512286
	Weighted median	36	0.919290098	1.00(0.98 to 1.02)		
	Inverse variance weighted	36	0.778079741	1.00(0.99 to 1.02)	0.05463038	
	Simple mode	36	0.904500185	1.00(0.97 to 1.04)		
	Weighted mode	36	0.890230455	1.00(0.97 to 1.03)		
Chronotype	MR Egger	131	0.156717702	1.01(1.00 to 1.02)	0.05549739	0.2389013
	Weighted median	131	0.384934919	1.00(1.00 to 1.00)		
	Inverse variance weighted	131	0.253307678	1.00(1.00 to 1.00)	0.0519769	
	Simple mode	131	0.988551132	1.00(0.99 to 1.01)		
	Weighted mode	131	0.772897793	1.00(0.99 to 1.01)		
Snoring	MR Egger	39	0.970352670	1.00(0.98 to 1.02)	0.143219	0.7294461
	Weighted median	39	0.573143634	1.00(1.00 to 1.00)		
	Inverse variance weighted	39	0.018835864	1.00(0.99 to 1.00)	0.1666103	
	Simple mode	39	0.072513614	0.99(0.98 to 1.00)		
	Weighted mode	39	0.931571087	1.00(0.99 to 1.01)		
Sleep apnoea	MR Egger	3	0.392134604	1.02(0.99 to 1.04)	0.2400198	0.4226853
	Weighted median	3	0.576935082	1.00(1.00 to 1.00)		
	Inverse variance weighted	3	0.418222441	1.00(1.00 to 1.01)	0.162409	
	Simple mode	3	0.682529379	1.00(0.99 to 1.00)		
	Weighted mode	3	0.153404029	1.00(1.00 to 1.01)		
Trouble falling asleep	MR Egger	4	0.737393437	0.98(0.90 to 1.07)	0.9950689	0.6986972
	Weighted median	4	0.128617226	1.00(1.00 to 1.01)		
	Inverse variance weighted	4	0.065832646	1.00(1.00 to 1.01)	0.9760277	
	Simple mode	4	0.378994952	1.00(1.00 to 1.01)		
	Weighted mode	4	0.380312930	1.00(1.00 to 1.01)		

P<0.005 was considered statiscally significant

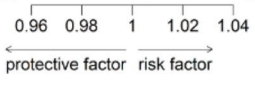

Fig. 2 Mendelian randomization estimation for causality of sleep traits on revision of knee arthroplasty

the MR-PRESSO. Furthermore, there was no significant heterogeneity or pleiotropy among the instrumental variable effects. A diagram of the above MR analysis results for the scatter plot of SNP effects, leave-one-way analysis, forest plot, and funnel plot are displayed in Figs. 3 and 4. However, the results of MR analysis revealed no causal relationships between the other sleep traits and revision after knee arthroplasty.

Causality between knee arthroplasty revision and sleep traits

We investigated potential reverse causal relationships between sleep traits and revision of knee arthroplasty using two-sample reverse MR. Specifically, we employed the IVW, MR–Egger, weighted median (WME), weighted mode, and simple mode methods to analyze independent genetic associations. As shown in Fig. 5 and Supplementary Table S2, the IVW analysis revealed no statistically significant evidence of reverse causation. Consistent with this, the MR–Egger, WME, weighted mode, and simple mode approaches did not demonstrate any significant reverse relationships between genetic predictors of revision of knee arthroplasty and sleep traits either.

Discussion

Principal findings

To the best of our knowledge, this was the first study to use various MR methods to explore the bidirectional causal link between sleep traits and revision after knee arthroplasty. In this study, we employed the largest GWAS summary-level dataset available to date from various sources to perform a two-sample MR analysis to fully investigate the causative effect of sleep traits on revision after knee arthroplasty. The MR analysis revealed a role of sleep duration in decreasing the risk of knee arthroplasty revision and a promoting role of short sleep duration in knee arthroplasty revision. In contrast, there was no causal relationship between the other eight sleep phenotypes and knee arthroplasty revision. In addition, no causal relationship was detected between sleep traits and other arthroplasty surgeries.

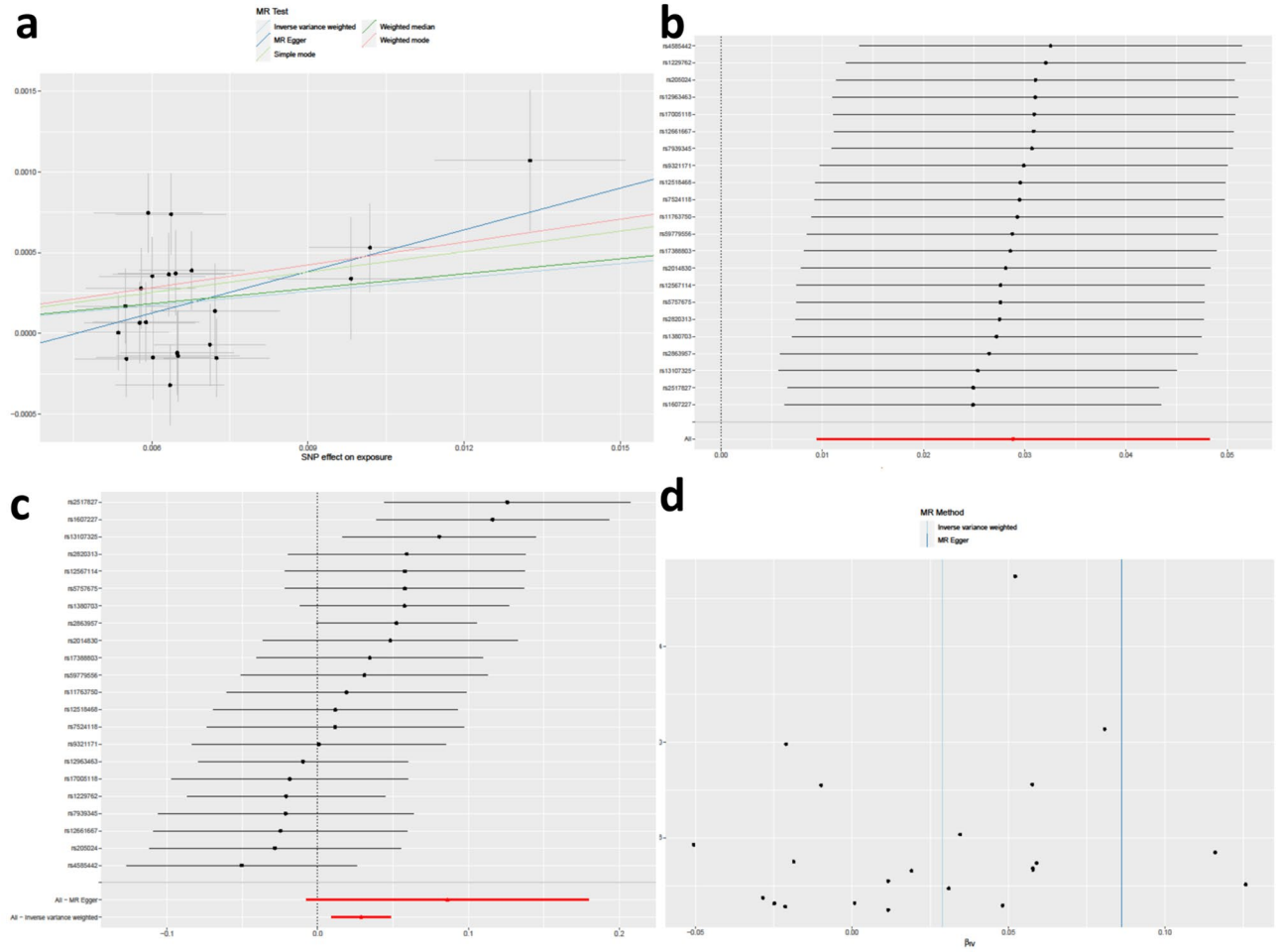

Fig. 3 Scatterplots of sleep duration based on SNP effect (**a**), one-way analysis (**b**), forest plot (c), and funnel plot (d)

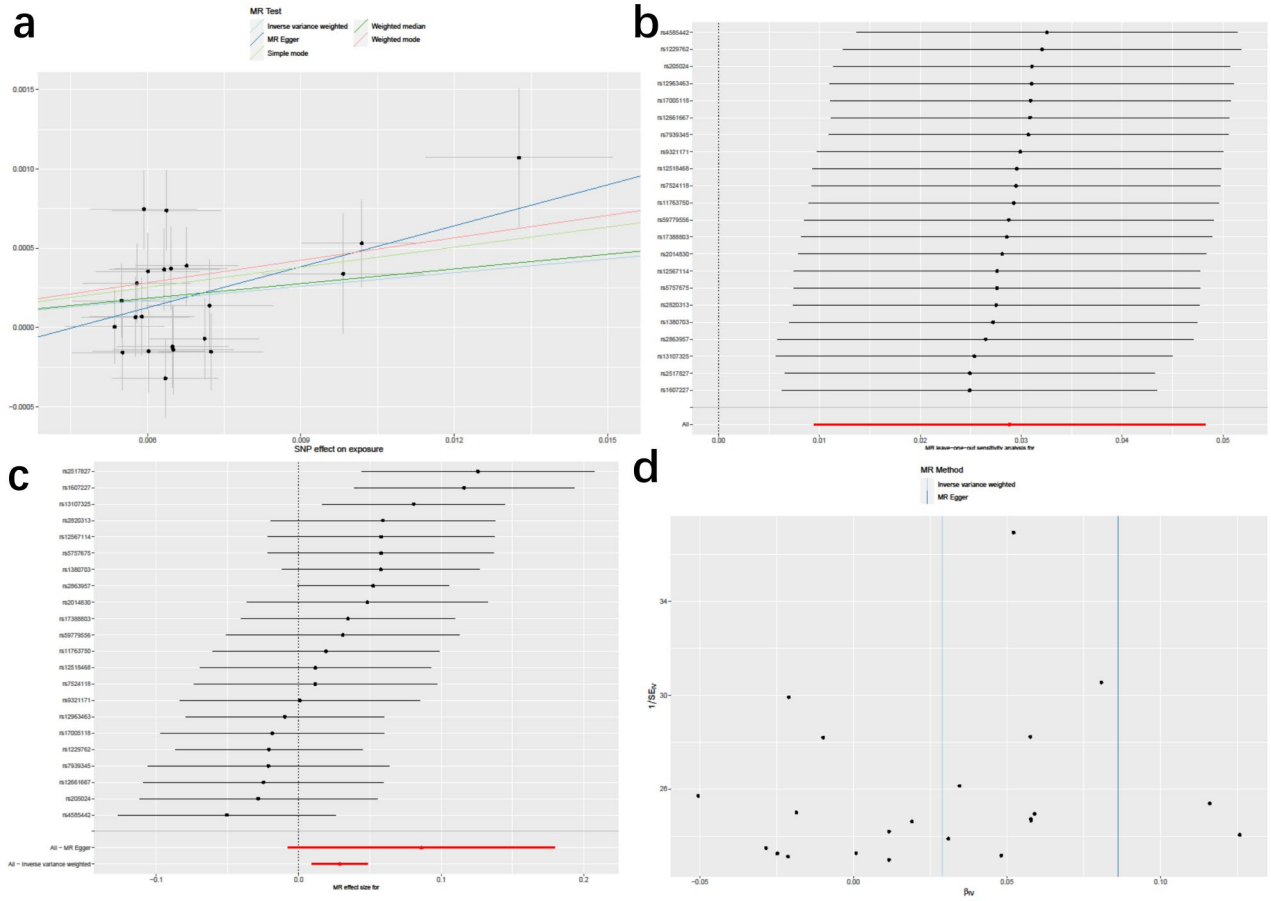

Fig. 4 Scatterplots of SNP effects based on sleep duration (**a**), one-way analysis (**b**), forest plots (c), and funnel plots (d)

Comparison with other studies

The associations between sleep traits and the outcome of knee arthroplasty were inconsistent across the reported studies. Furthermore, prior studies did not directly examine the relationship between sleep traits and risk for knee arthroplasty revision using MR analysis. In view of this, our MR analysis was novel for exploring the potential causal role of sleep characteristics in knee arthroplasty revision. For instance, observational research has suggested that bodily function and pain interference are strongly associated with sleep disturbance and dyspnea after joint arthroplasty, but the causation between sleep disturbance and joint arthroplasty revision has not been explored [55]. Our IVW and weighted median estimates demonstrated a significant causal association between sleep duration and revision of knee replacement. In a randomized clinical trial involving 148 patients, Gong et al. suggested that sleep time was significantly correlated with the range of motion after TKA [24]. Conversely, several retrospective investigations concluded that sleep duration did not correlate with any clinical variables and did not appear to be a meaningful metric for measuring TKA outcomes; however, these studies examined outcomes only within the first 90 days after surgery [20].

A longitudinal TKA study showed a significant relationship between insomnia 2 weeks before TKA and postoperative pain and functional outcomes [56]. Daytime napping could provide an opportunity to augment night-time sleep, which might promote the recovery of physical and mental performance [57]. However, our MR analysis did not find any causal correlation between insomnia, daytime napping, chronotype, or knee arthroplasty revision. One potential reason for the inconsistent results in those GWAS data might be the low sensitivity of the self-reported phenotypic data, indicated by categorical variables such as never/sometimes/usually or yes/no. It is important to mention that categorical data are not amenable to quantitative analysis, as it does not allow for numerical or arithmetic operations. Moreover, daytime sleepiness was demonstrated to be uncorrelated with postoperative outcomes and complications [58], which was consistent with our MR results.

We found no causal role of sleep apnea or snoring in the revision of knee arthroplasty. This finding was contrary to that of a previous study, which indicated that

Outcome	Method	nSNPs	p.value	OR(95%CI)	Heterogeneity.Test.P	Pleiotropy.Test.P
Sleep duration	MR Egger	18	0.3949903	5.05e-03(0.00 to 7.13e+02)	16 1.705028e-05	0.4465936
	Weighted median	18	0.2271572	4.84e-01(0.15 to 1.57e+00)		
	Inverse variance weighted	18	0.3207944	5.54e-01(0.17 to 1.78e+00)	17 1.571825e-05	
	Simple mode	18	0.2179979	1.59e-01(0.01 to 2.66e+00)		
	Weighted mode	18	0.3564982	3.48e+00(0.26 to 4.57e+01)		
Short sleep duration	MR Egger	19	0.3104101	1.55e+01(0.09 to 2.63e+03)	0.01892387	0.327478
	Weighted median	19	0.5937232	8.57e-01(0.49 to 1.51e+00)		
	Inverse variance weighted	19	0.6766574	1.12e+00(0.66 to 1.89e+00)	0.01642592	
	Simple mode	19	0.2558864	5.02e-01(0.16 to 1.59e+00)		
	Weighted mode	19	0.2366544	5.02e-01(0.17 to 1.51e+00)		
Long sleep duration	MR Egger	19	0.9197912	8.53e-01(0.04 to 1.79e+01)	0.3188291	0.9306634
	Weighted median	19	0.5904182	1.12e+00(0.75 to 1.67e+00)		
	Inverse variance weighted	19	0.8849477	9.78e-01(0.72 to 1.32e+00)	0.3808565	
	Simple mode	19	0.8546914	1.07e+00(0.52 to 2.20e+00)		
	Weighted mode	19	0.9085931	1.04e+00(0.51 to 2.12e+00)		
Insomnia	MR Egger	19	0.7544290	2.93e+00(0.00 to 2.20e+03)	0.09604219	0.7752327
	Weighted median	19	0.4104103	1.41e+00(0.62 to 3.21e+00)		
	Inverse variance weighted	19	0.7681699	1.10e+00(0.57 to 2.13e+00)	0.12315518	
	Simple mode	19	0.3380033	2.35e+00(0.43 to 1.29e+01)		
	Weighted mode	19	0.3793375	2.23e+00(0.39 to 1.27e+01)		
Daytime napping	MR Egger	19	0.2926117	7.29e+01(0.03 to 1.68e+05)	0.000308702	0.328256
	Weighted median	19	0.1160307	1.88e+00(0.86 to 4.13e+00)		
	Inverse variance weighted	19	0.4064429	1.40e+00(0.63 to 3.08e+00)	0.000215582	
	Simple mode	19	0.2008806	3.24e+00(0.57 to 1.84e+01)		
	Weighted mode	19	0.2852256	2.43e+00(0.50 to 1.17e+01)		
Daytime sleepiness	MR Egger	19	0.7275751	3.58e+00(0.00 to 4.17e+03)	2.76536E-05	0.652758
	Weighted median	19	0.2408618	6.78e-01(0.35 to 1.30e+00)		
	Inverse variance weighted	19	0.3092988	6.94e-01(0.34 to 1.40e+00)	3.99934E-05	
	Simple mode	19	0.5722331	6.85e-01(0.19 to 2.49e+00)		
	Weighted mode	19	0.4895624	6.71e-01(0.22 to 2.04e+00)		
Chromptype	MR Egger	19	0.3959610	5.29e+02(0.00 to 7.11e+08)	0.02624402	0.3393049
	Weighted median	19	0.7261901	7.38e-01(0.13 to 4.04e+00)		
	Inverse variance weighted	19	0.2931367	4.62e-01(0.11 to 1.95e+00)	0.02624402	
	Simple mode	19	0.9878684	1.03e+00(0.03 to 3.31e+01)		
	Weighted mode	19	0.9708417	1.07e+00(0.03 to 3.70e+01)		
Snoring	MR Egger	18	0.8704982	8.72e-02(0.00 to 2.98e+11)	0.00092258	0.9712748
	Weighted median	18	0.1859466	1.21e-01(0.01 to 2.77e+00)		
	Inverse variance weighted	18	0.0472013	5.11e-02(0.00 to 9.64e-01)	0.001523072	
	Simple mode	18	0.6082069	2.45e-01(0.00 to 4.83e+01)		
	Weighted mode	18	0.5815409	2.45e-01(0.00 to 3.33e+01)		
Sleep apnoea	MR Egger	18	0.4088300	7.62e+10(0.00 to 1.06e+36)	0.6625807	0.4868065
	Weighted median	18	0.4350203	1.83e+01(0.01 to 2.68e+04)		
	Inverse variance weighted	18	0.1168695	6.10e+01(0.36 to 1.04e+04)	0.6920124	
	Simple mode	18	0.9459355	6.40e-01(0.00 to 2.11e+05)		
	Weighted mode	18	0.9199373	1.92e+00(0.00 to 5.07e+05)		
Trouble falling asleep	MR Egger	18	0.1419216	8.84e+18(0.00 to 9.63e+42)	0.4712533	0.1568233
	Weighted median	18	0.7596362	3.42e+00(0.00 to 9.04e+03)		
	Inverse variance weighted	18	0.5308218	6.72e+00(0.02 to 2.60e+03)	0.3921959	
	Simple mode	18	0.4270066	6.85e-04(0.00 to 2.86e+04)		
	Weighted mode	18	0.3979554	3.64e-04(0.00 to 2.16e+04)		

P<0.005 was considered statiscally significant

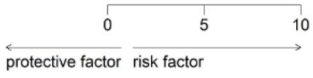

Fig. 5 Mendelian randomization estimation for causality between revision of knee arthroplasty and sleep traits

joint arthroplasty patients with sleep apnea had greater odds of revision surgery [14]. However, this study was retrospective and included data on the rate of joint revision over a two-year period alone. We hypothesized that the discrepancy between the current MR results and observational findings might derive, in part, from limitations of observational research, follow-up time, and different ancestral bloodlines. Moreover, patients with sleep apnea were more likely to experience pulmonary complications after TJA [59], which was contrary to the findings reported by Shen et al. and Thompson et al. They found the rate of postoperative cardiopulmonary problems was low in patients who underwent joint arthroplasty and the patients had a high risk of sleep apnea [60]. However, the causal relationship between joint arthroplasty and sleep apnea remains unclear. Accordingly, prospective studies with longer-term data are necessary to

investigate the association between sleep apnea and outcomes following arthroplasty.

Our reverse MR analysis exhibited that knee arthroplasty revision did not exert a notable effect on sleep traits, which was partially consistent with the findings of an observational cohort study in which sleep amount and timing parameters remained steady throughout hospital stay [61]. Additionally, a prospective study indicated that TKA patients had poor sleep quality both preoperatively and postoperatively after excluding patients with a history of sleep disturbance. The daily use of exogenous melatonin did not have any noteworthy impact on sleep quality [62]. These findings implied that sleep disturbances observed in prior observational studies before and after surgery might have been transient and related to the surgical procedure itself rather than long-term risk exposure or postoperative outcomes.

Identifying risk factors for revision surgery is challenging due to various factors. First, the high survival rates associated with total knee replacement (TKA) implants at 10 years (95.8–96.6%) and 20 years (89.7%, 87.5–91.5%) made it difficult to gather accurate information on revisions [63]. Most of the included articles had follow-up periods of less than 10 years. Conducting studies of appropriate duration to obtain precise revision data can thus be both time-consuming and expensive. Multiple factors contributed to the inconsistency of the findings between the MR analysis and observational study. First, the change in sleep-traits, in most cases, did not suffice to entail an arthroplasty revision in within a short period. Second, these studies had short review or follow-up periods, small sample sizes, and selection bias, resulting in missing of patient data. Moreover, arthroplasty cases were not included in the outcome study. Third, some patients experienced transient sleep disturbances related to surgery, which could improve or worsen after the procedure [23]. Fourth, previous studies often attributed all sleep problems to overall sleep quality, overlooking the specific impacts of various sleep traits on post-TKA outcomes. Thus, there is a crucial need to break down and separately examine the specific effects of sleep characteristics on post-TKA patients to gain a comprehensive understanding of these effects in prospective clinical studies [64]. Finally, observational studies rely on self-reported symptoms in surgical patients, which can be influenced by social, psychological, and surgical factors, leading to confounding variables. This Mendelian study attempted to minimize these confounding factors. In summary, identifying risk factors for revision surgery after knee replacement surgery is challenging due to the high survival rate of patients and the various confounding factors identified in previous studies.

Clinical significance and possible mechanisms

Clinical significance

The identification of significant differences between sleep duration and the need for revision surgery, as elucidated through Mendelian randomization, highlights a potentially causal relationship warranting meticulous analysis. These results implied that variations in sleep duration might have a consequential effect on the probability of requiring revision knee arthroplasty, underscoring the critical role of sleep patterns in both postoperative recovery and longevity of the implant. However, further exploration is needed to ascertain the extent of this effect and to decipher the underlying biological mechanisms. However, preliminary evidence suggested that enhancing sleep quality could be an innovative preventive measure, possibly reducing the incidence of revision surgeries. This proposition not only heralds new opportunities for improving patient outcomes via lifestyle modifications but also necessitates further empirical studies to corroborate these initial findings and to incorporate sleep management strategies into the clinical guidelines for knee arthroplasty care.

Moreover, the application of genetic data in Mendelian randomization provides a solid foundation for confirming causality, facilitating the development of interventions with the potential to markedly influence the clinical management and prognosis of individuals undergoing knee replacement procedures. This approach emphasizes the importance of a comprehensive understanding of the interplay between genetic factors and lifestyle behaviors, such as sleep, from the perspective of surgical outcomes and patient health.

Possible genetic pathways

In this MR analysis, we used specific SNPs as instrumental variables to delineate the causal relationship between sleep duration and the risk for knee arthroplasty revision. Our study suggested that the SNPs might constitute a locus of genetic variation with the potential to modulate biological processes. In the ensuing discourse, we discuss the contributory roles of selected SNPs, such as rs12661667 and rs11763750, to demonstrate how the manner in which genetic predispositions associated with sleep traits may influence postoperative prognoses.

The SNP rs12661667 is located within the USP49 gene and is implicated in the suppression of the PIK3R2/AKT signaling pathway [65]. The attenuation of the PIK3R2/AKT pathway has been shown to induce oxidative stress subsequent to chronic sleep deprivation [66]. Furthermore, USP49 has been linked to the modulation of circadian rhythms, potentially impacting both sleep duration and quality [35]. Perturbations in circadian regulation are known to be associated with inflammatory processes that may retard recovery and amplify the risk of postoperative

complications in knee arthroplasty patients. Additionally, the variant rs11763750, residing within the MAD1L1 gene, is correlated with systemic inflammation [67]—a pivotal determinant of both the recuperation and enduring success of joint replacement interventions.

On the basis of the biological functionality of the SNPs, we proposed a tentative genetic schema that illuminates the molecular interactions possibly underpinning the correlation between sleep duration and the incidence of revision after knee arthroplasty. It must be acknowledged, however, that this exposition is conjectural and contingent upon the extant corpus of knowledge that is subject to evolution with the advent of new empirical evidence. Consequently, prospective functional investigations are needed to substantiate these postulated associations and explicate the mechanisms whereby genetic variations related to sleep may change surgical outcomes.

Possible mechanisms

A short sleep duration has been linked to various physiological and psychological factors that may impact TKA outcomes and increase the risk for revision. One potential mechanism is the effect of insufficient sleep on pain perception. Inadequate sleep has been associated with reduced pain tolerance, hyperalgesia, and central sensitization [68]. In the context of TKA, individuals with shorter sleep durations may have increased pain levels [16], leading to dissatisfaction and a greater likelihood of revision surgery.

Furthermore, inadequate sleep can disrupt the body's natural healing processes. Sleep plays a crucial role in tissue repair and metabolic rate [69]. Insufficient sleep may hinder these processes and aggravate systemic inflammation [70], resulting in delayed wound healing, impaired tissue regeneration, and compromised overall recovery from TKA. As a result, individuals with short sleep durations may experience prolonged recovery periods and an increased risk for complications, potentially necessitating revision surgery.

Moreover, sleep deprivation can impact cognitive function and decision-making abilities. A lack of sleep has been found to be associated with cognitive impairments, including reduced attention, impaired memory and fatigue [71]. TKA patients with impaired cognitive function may struggle to adhere to postoperative care instructions, such as medication schedules, physical therapy exercises, and weight-bearing restrictions [72]. Non-compliance with these essential aspects of recovery can lead to suboptimal outcomes and a greater risk for revision.

In addition, short sleep durations are associated with fewer naive T cells [73] and a weakened immune system, which could increase susceptibility to infections [74]. Moreover, infections are among the most common causes of knee arthroplasty revision.

Additionally, sleep disturbances, including anxiety and depressive disorders, have been identified as contributing factors to the development of psychological distress [75]. Prior research has consistently shown that depression and anxiety have deleterious effects on well-being across a wide range of demographic groups, irrespective of race, geographical location, or sex [76–80]. Post-TKA patients with short sleep durations may be more prone to these psychological conditions, which can negatively impact their overall well-being and recovery. Furthermore, psychological distress was found to be linked to inferior surgical outcomes and an increased utilization of healthcare resources [81], potentially elevating the risk of requiring revision surgery. This body of evidence underscores the importance of addressing sleep disturbances and psychological well-being as an integral component of postoperative care to improve patient outcomes and reduce the burden on healthcare systems.

In summary, several mechanisms can explain how short sleep duration may contribute to knee arthroplasty revision. These include heightened pain perception, impaired healing and recovery, a weakened immune response, inflammation, cognitive impairments affecting adherence to postoperative care, and the development of psychological distress. However, further research is necessary to better comprehend the complex mechanism linking sleep traits and TKA outcomes. This understanding will help improve patient care and potentially reduce the rate of revision surgery. The potential underlying mechanisms are shown in Fig. 6.

Strengths and limitations

Mendelian randomization (MR) is an analytical method utilized in epidemiology that employs genetic variants as instrumental variables to estimate the causal effect of an exposure on an outcome. This approach offers a powerful tool for causal inference and has several distinct advantages and limitations. One of the key strengths of MR is its ability to reduce the impact of confounding factors compared to traditional observational studies. This is achieved through the random assignment of genetic variants at conception. Consequently, the allocation of these variants mimics the conditions of a randomized controlled trial, ensuring that the genetic variants associated with the exposure of interest are not influenced by confounding variables [82]. Another crucial aspect of MR is its capacity to establish a clear temporal relationship between the exposure and the outcome. MR addresses concerns regarding reverse causation, a phenomenon that can complicate the interpretation of observational studies. By employing genetic variants as proxies for exposures, MR helps mitigate the uncertainty

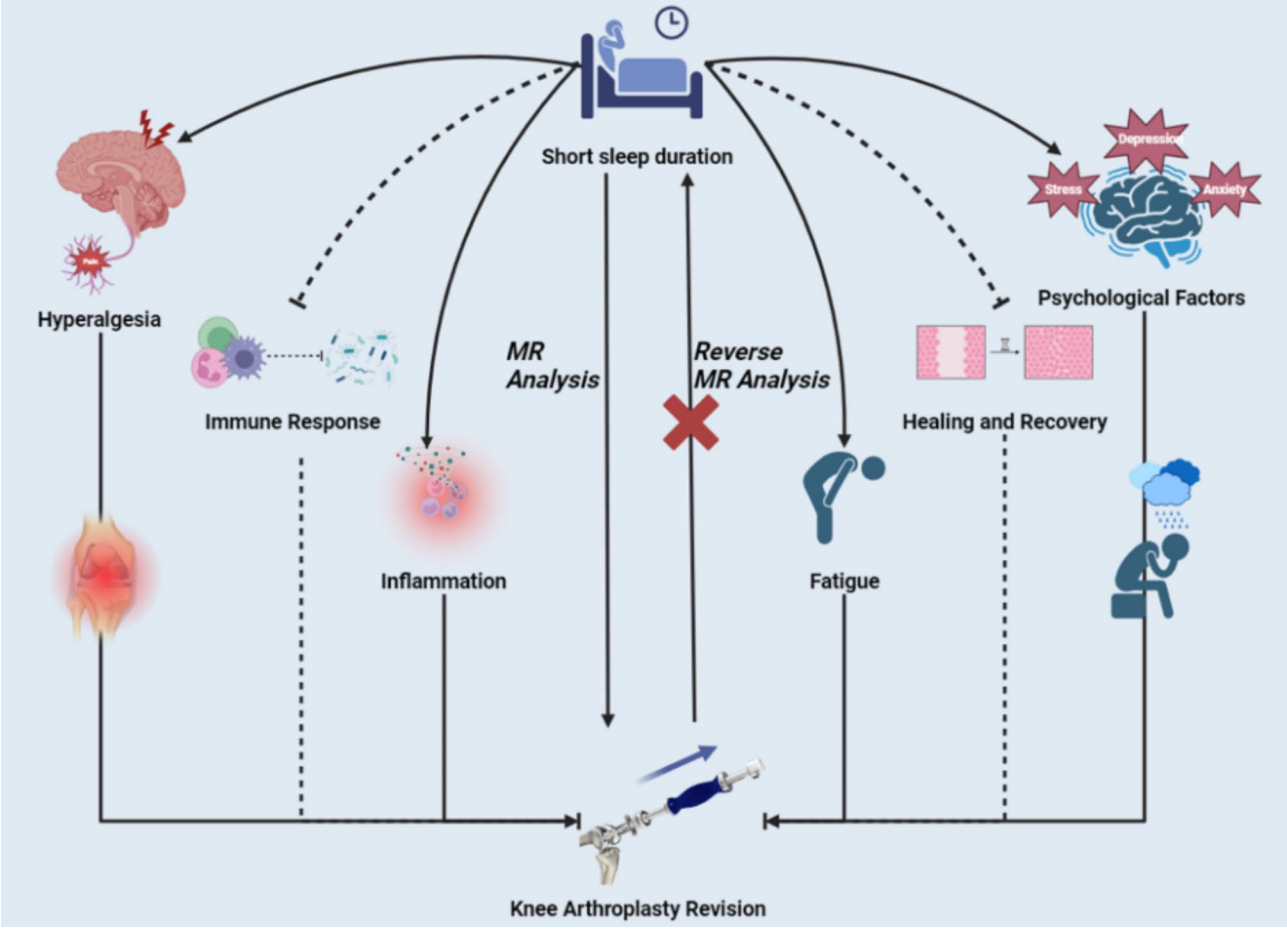

Fig. 6 Graphic abstract. Bidirectional causal relationships between sleep traits and knee arthroplasty revision and potential underlying mechanisms. This MR study provided limited evidence supporting the use of sleep-improving strategies for preventing knee arthroplasty revision. Moreover, the findings added to the evidence that knee arthroplasty revision does not exert effect on sleep traits. MR: Mendelian randomization

surrounding whether the exposure affects the outcome or vice versa. This approach provides a more robust framework for drawing causal inferences [30]. Furthermore, MR is extensively applicable because it can be effectively employed to investigate the causal effects of exposures that are challenging to manipulate in randomized trials due to ethical, practical, or financial constraints. This approach has widened the scope of related research and has facilitated the examination of various exposures and outcomes [83].

With regard to Mendelian randomization studies, the Instrumental Variable method, notably the IVW approach, is a primary methodology for estimating the causal effect of an exposure on an outcome. Despite the fact that it effectively facilitates causal inference, the IVW method is susceptible to several biases that can compromise the validity of its estimates. One such bias is pleiotropy, which arises when the genetic variants serving as instruments influence the outcome through pathways unrelated to the exposure of interest. Horizontal pleiotropy can distort IVW estimates if genetic variants impact the outcome via alternative risk factors. To detect and correct for pleiotropic effects, sensitivity analyses, including MR–Egger regression, were employed [84]. Another challenge is weak instrument bias, which occurs when the genetic variants employed as instruments account for a minimal proportion of the variance in the exposure. Such scenarios can lead to estimates that bias toward observational associations, which are potentially confounding. This issue is commonly evaluated using the F-statistic, with an F-statistic less than 10 indicating a possibly weak instrument [85]. Selection bias represents another potential concern, as it emerges when the study population does not reflect the general population due to the selection criteria applied. For instance, a propensity to include individuals possessing both the exposure and outcome may skew the IVW estimates [86]. Additionally, overlapping samples can introduce bias. Specifically, utilizing the same individuals to estimate genetic associations with both the exposure and the outcome can result in overfitting and, consequently, biased estimates—a phenomenon referred to as "sample overlap bias". Employing

non-overlapping samples for the analyses of exposure and outcome associations can mitigate this issue [87]. Last, the dynamic consequences of the exposure on the outcome, such as effects that vary over time or are contingent upon the exposure level, pose a challenge. Linear models such as IVW may not adequately capture these complex relationships, potentially leading to biased estimates [88].

In addition, this study is also subject to other potential limitations. First, the validity and sensitivity of the results were not ascertained in some GWASs since they used categorical variables and self-reported sleep phenotypes rather than objective sleep assessments. Second, estimates from previous studies might not be similar to those from observational studies since genetic variants used as a proxy for exposure reflect exposure across a lifetime rather than the exposure at a single measuring occasion. Third, as the summary statistics we used were based primarily on one cohort, the results for knee arthroplasty revision and short sleep duration may be skewed by the winner's curse. Future studies should include robust replication of these findings. Fourth, the synergistic effects of chronotype, snoring, sleep duration, sleep apnea, and insomnia on knee arthroplasty need further investigation. Additional studies are warranted to determine the roles of sleep phenotypes. Besides, the database utilized for our Mendelian Randomization (MR) study lacks specific classifications for the reasons behind TKA revisions and sleep traits, which restricted our analysis to broader categorizations of sleep phenotypes and joint revision without delving into the specific etiological factors in question. The dataset we utilized did not include detailed patient characteristics such as gender, age, BMI, or the timing of prosthesis revision. Future studies need to incorporate more detailed classification and longitudinal data to provide deeper insights into these relationships as the GWAS database develops. Finally, accessing data bias may occur if the study population is not representative of the general population. Population stratification can skew results in MR studies [89, 90]. Using within-family MR [91], which analyzes data from family members like sibling pairs or parent-child trios, helps control these biases by accounting for genetic variations within families [90]. However, this approach is limited by the scarcity of family-based GWAS data [30]. Expanding family-based GWAS could improve MR's accuracy by integrating family structures, thus enhancing causal inferences [92]. To minimize this, we used GWAS summary statistics from large, well-characterized cohorts of European ancestry, which reduces the potential for population stratification. Meanwhile, we have taken some steps to ensure data integrity, such as sensitivity analyses, including MR-Egger regression, to detect and correct for pleiotropic effects and calculated F-statistics to evaluate and mitigate weak instrument bias. We also used non-overlapping samples to minimize sample overlap bias. However, we acknowledge that future studies should aim to include diverse populations, and collecting more family-level data is vital to develop this method further and address stratification issues in conventional MR.

Despite these limitations, Mendelian randomization continues to be a valuable tool in the arsenal of epidemiological methods for causal inference. It serves as a complementary approach to traditional observational studies and randomized controlled trials, offering unique insights that may be difficult to obtain through alternative means. First, the large sample sizes achieved through our two-sample MR approach, combined with the use of genetic variants as instrumental variables, reduced susceptibility to reverse causation and residual confounding relative to conventional observational studies. Second, examining only exposures genetically predicted from European populations avoided potential bias from confounding by demographic factors such as ancestry. This strengthens the internal validity of the findings. Finally, the analyses were controlled for horizontal pleiotropy and heterogeneity across genetic variants through multiple sensitivity analyses, adding to the robustness of the conclusions regarding causal effects. In summary, the key strengths included the MR study design, large homogeneous sample, and sensitivity analyses controlled for potential validity threats. Moreover, the current analysis utilized extensive publicly available GWAS data, which provided a substantial sample size. This large sample size enhanced the power of our study, allowing for reliable estimation of lifelong causality.

Conclusion

In general, our study involved two-sample MR analyses, which yielded comprehensive screening data on the causal associations between sleep traits and revision after knee arthroplasty. However, reverse MR analysis did not establish a causal link between knee arthroplasty and sleep traits. These findings highlighted the crucial role of sleep duration in the knee arthroplasty revision. Understanding this correlation has significant clinical implications, since short sleep duration (average sleep duration of 24 h is 6 h or less) has been identified as a potential therapeutic target for preventing knee arthroplasty revision.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-024-05031-0.

Additional File 1: Supplementary Tables.

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Author contributions
Z.B.: Conceived and presented the idea of the study; Z.B. & Y.C.: processed the data and wrote the manuscript; Y.C.: participated in the acquisition and interpretation of the data. All the listed authors have made significant intellectual contributions to the research, approved its claims and agreed to be listed as authors. All authors have read and approved the final manuscript.

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Data availability
The data used in the MR analyses were publicly available and did not require specific ethical approval. The summary GWAS data of the sleep-related traits are available at: https://www.ebi.ac.uk/gwas/home and http://sleepdisordergenetics.org/. The summary statistics concerning the knee arthroplasty revision GWAS are available at: https://gwas.mrcieu.ac.uk/.

Declarations

Ethics approval and consent to participate
The current MR investigation did not require specific ethical approval because it used publicly accessible summary data. The studies were conducted with the approval of the respective institutional ethical review boards and in accordance with the Declaration of Helsinki.

Consent for publication
All the participants in our study provided consent for publication.

Competing interests
The authors declare no competing interests.

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