Sleep and degenerative skeletal disorders: an Observational and Mendelian randomization study

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Research Article

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Abstract

Objectives: Skeletal degeneration is influenced by genetics, environment and lifestyle, but the role of sleep in its development remains uncertain. This study investigates the association between sleep and the risk of degenerative skeletal disorders, aiming to identify the impact of specific sleep characteristics on skeletal disorder phenotypes.

Methods: The observational study utilized health data from 387,822 UK Biobank participants. Cox proportional risk regression estimated the association between sleep and degenerative skeletal disorders. Two-sample MR analyses validated the bidirectional causal relationships based on genetic associations summary data of sleep characteristics from UK Biobank and skeletal disorders from FinnGen as well as meta GWAS, using inverse-variance weighted (IVW), MR-PRESSO, weighed median and MR-Egger.

Results: In observational study, 37 pairs of exposure-disease risk associations were identified between six sleep characteristics and eight degenerative skeletal phenotypes. The risk of degenerative skeletal disorders was increased with unhealthy sleep characteristics. MR analysis confirmed four robust causality associations: short sleep duration with overall OA (OR=2.88, 95%CI: 1.63-5.07), knee OA (OR=2.50, 95%CI: 1.33-4.68), and LDD (OR=2.97, 95%CI: 1.63-5.41), and long sleep duration with LDD (OR=0.13, 95%CI: 0.03-0.53). Four positive associations were considered potentially causal, including insomnia with LDD and spondylosis, early chronotype with overall OA, and short sleep duration with CDD.

Conclusions and Relevance: Large prospective observational and MR studies suggest a causal effect of sleep on spine and peripheral joint degeneration, emphasizing the value of sleep management in ameliorating joint degeneration.

Introduction

Degenerative skeletal disorders are common and serious illnesses, including osteoarthritis (OA), intervertebral disc degeneration (IDD), and osteoporosis (OP) [1]. OA and IDD are the primary causes of waist and joint pain, as well as disability in the elderly [2, 3]. OP is the major contributor to fractures and refractures, especially among postmenopausal women [4]. It is reported that more than 500 million people worldwide are affected by OA, approximately 700 million suffer from low back pain associated with IDD, and more than half of all women will sustain one or more osteoporosis-related fractures in their lifetime [5-7]. What’s more, Studies have shown that the incidence of degenerative skeletal disorders is steadily increasing, with a projected overall prevalence increase of at least 50% by 2050 [8]. The high disability rates and rehabilitation costs associated with skeletal degeneration pose significant burdens and challenges to public health [9-12]. Skeletal degeneration is a complex process influenced by several factors, including injury, pre-existing diseases (such as metabolic diseases), genetic factors, and environmental factors [13, 14]. In addition to these risk factors that have been widely verified, sleep disorders caused by intense work pressure, and shift work also need to pay more attention [15]. Sleep disorders are increasingly
becoming a prevalent health issue, affecting both young individuals and the elderly, and research has indicated that sleep disorders are associated with various bone health\cite{16-18}.

However, previous research evidence on sleep and degenerative bone disorders is fraught with controversy. Observational studies have shown that sleep disorders are associated with reduced bone density and an increased risk of OP, particularly in women\cite{19}. Sleeping less than 7 hours per day was significantly associated with an increased risk of OP compared to sleeping 9 hours or more per day\cite{20, 21}. Contrary, another pooled result of meta-analyses has indicated that sleeping more than 8 hours per day is also associated with an increased risk of OP\cite{22, 23}. Regarding OA and IDD, although research also reported a positive association between sleep disorders and the risk of these two diseases, the findings from different studies are conflicting\cite{24-26}. Heterogeneity among the evidence may arise primarily from differences in study design and exposure definitions. First, most of the studies were population-based cross-sectional studies. Second, some studies used sleep apnea syndrome as an exposure factor for sleep disorders, which introduced potential confounding factors that may bias the association\cite{27, 28}. Thirdly, establishing causal inference is challenging due to the limitations of observational studies. Moreover, few studies have examined the impact of sleep characteristics, such as insomnia, chronotype (morning or evening preference), daytime sleepiness, etc., on skeletal degeneration.

Therefore, adopting novel methods to clarify the association between sleep and skeletal degeneration will contribute to develop better precautions. Mendelian randomization (MR) study is an appropriate alternative compared with observational studies, which employs genetic variation as an instrumental variable to ascertain whether exposures have a causal impact on health outcomes\cite{29, 30}. The genetic variants selected in MR studies are specifically chosen based on their association with exposure factors rather than outcomes. Thus, this method can effectively minimize the impact of potential confounding factors\cite{31-33}. In addition, the UK Biobank is a vast prospective cohort consisting of more than 500,000 participants. It encompasses comprehensive health and genetic information of the participants and serves as a valuable source of sample data for studies examining the association between exposure and disease\cite{34}. In this study, we firstly investigated the relationship between sleep characteristics and skeletal degeneration using data from the UK Biobank cohort. Secondly, we examined whether there is a causal link between sleep characteristics and skeletal degeneration by utilizing genetic variants associated with sleep characteristics (Figure 1). To address the second objective, we conducted a two-sample MR analysis, comparing the findings with those obtained from traditional observational multivariable regression analysis. The reporting of this paper adhered to the STROBE-MR reporting guidelines\cite{30}.

**Materials and methods**

**Study design**

We first investigated the association between sleep characteristics and the risk of degenerative skeletal disorders in the UK Biobank using Cox regression analysis. We also conducted stratified and interaction
analyses according to the skeletal disorders polygenic risk scores (PRS). Then, we further verified the causal associations between sleep characteristics and degenerative skeletal disorders using bidirectional two-sample MR.

**Acquisition of GWAS data**

For skeletal disorder, the genome-wide association summary statistic data of overall OA, hip OA, knee OA, CDD, LDD, OP, spondylosis were obtained from the release version 9 of FinnGen (https://r9.risteys.finngen.fi/)\(^{[35]}\), and data of hand OA was obtained from the largest published GWAS of hand OA until now, with 303,782 samples (case: 20,901, control: 282,881)\(^{[36]}\). Summary statistic data of sleep characteristics were all obtained from the Sleep disorder knowledge portal (SDKP) (https://sleep.hugeamp.org/). All the included studies were based on UK Biobank populations. Genetic associations of insomnia were obtained from the GWAS with 109548 cases and 277440 controls, which was published by Watanabe K, et al. at 2022\(^{[37]}\). Data of early chronotype\(^{[33]}\), daytime sleepiness\(^{[38]}\), short sleep duration (< 7h) and long sleep duration (≥ 9h)\(^{[39]}\) were obtained from studies of self-reported sleep traits in UK Biobank. Data of self-reported snore was from the GWAS study conducted by Campos AI, et al. at 2020\(^{[40]}\). Details of the description of all the GWAS datasets were available in supplemental data (Supplement 1).

**Observational study**

**Study participants and exposure factors:** We utilized participant data from the UK Biobank, a comprehensive health information collection from over 500,000 individuals aged 40-69 years. During the initial assessment at study inclusion, participants completed multiple touch-screen questionnaires covering sociodemographic status, lifestyle and environmental, health and medical history, and psychosocial factors. Additionally, participants provided information on various sleep characteristics, such as insomnia presence, chronotype (morning or evening), average sleep duration, and daytime sleepiness. We employed the latest sleep scoring system to assess each participant’s sleep quality, categorizing it as poor (0-1), moderate (2-3), or healthy (4-5) sleep patterns (Supplement 1).

**Outcomes:** We obtained information on the initial diagnosis of degenerative skeletal disorders (OA, OP, IDD) by referring to ICD-10 codes (international classification of diseases, 10th revision) (eTable 1 in the Supplement 1). In cases where participants had multiple diagnoses, we considered the first diagnosis. To ensure the accuracy of our analysis, we excluded participants who had pre-existing diagnostic information prior to the baseline. For participants without diagnostic information, we utilized death or the dates December 31, 2022 as the cutoff points for follow-up.

**Polygenic risk scores (PRS)** We construct PRS of skeletal disorders for UK Biobank populations. PRS were created following a weighted additive model, using common genetic variants associated with degenerative skeletal disorders extracted from GWAS data. Then, the best fitted PRS were stratified into low (lowest quartile), intermediate (quartile 2-3) and high (highest quartile) risk based on values for all
individuals. Details of the quality control of the GWAS data, genotyping, imputation and quality control of UK Biobank data, as well as construction and fitting of the PRS were provided in the supplemental data (Supplement 1).

Covariates: In order to examine the association between sleep and degenerative skeletal disorders, we took into account various potential confounders based on previous studies and literature review[41]. These included gender, age, alcohol intake, smoking, activity level, vitamin intake, and components of metabolic syndrome such as blood lipids, high-density lipoprotein (HDL), blood glucose, blood pressure, and obesity. We obtained information on these confounders through physical and blood measurements conducted at the beginning of the study, as well as through questionnaire responses.

Multivariable regression analysis Multivariable regression analysis was conducted to examine the relationship between sleep and the risk of degenerative skeletal disorders. Additionally, a joint analysis was performed to assess potential interactions between sleep patterns and genetic risk for degenerative skeletal disorders. The regression analysis models used in the study included basic models (adjusted only with age and gender), multivariable models (which added alcohol intake, smoking, activity level, and vitamin intake to the basic model), and fully adjusted models (which further added metabolic syndrome ingredients to the multivariable model). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (KS test). Baseline characteristics were described using percentages and frequencies for categorical variables, mean (standard deviation, SD) for normally distributed continuous variables, and median (interquartile range) for skewed variables. Finally, we used diagnostic sleep disorders (ICD-10: G47) as an exposure factor for a secondary replication of the observational study in the same cohort.

Mendelian randomization analyses

We further conducted bidirectional two-sample mendelian randomization analyses to identify the causal associations between six sleep characteristics and eight degenerative skeletal disorder phenotypes. Our MR study complied the three basic MR assumptions (Figure 1).

Selection of instrumental variables: In the bidirectional MR analyses, SNPs were selected as instrument variables (IVs) from the GWAS data of exposures, with a genome-wide significant threshold of $P < 5 \times 10^{-8}$ and frequency threshold of MAF > 1%. SNPs were then clumped with the linkage-disequilibrium threshold of $r^2 < 0.1$ within 1000kb distance, using the European reference panel from 1,000 Genome project[42]. After harmonised with outcome datasets, palindromic SNPs with MAF > 0.42 were excluded.

MR analyses: A two-stage design was used in our MR analyses. Firstly, we comprehensively scanned all potential causal associations using inverse-variance weighted (IVW) method, which assumes all genetic variants are valid IVs[43]. In order to control type I error, we applied False discovery rate (FDR) method for multiple comparison correction (N=48) : FDR< 0.05 was defined as the multiple corrected significant threshold, while FDR> 0.05 and $P< 0.05$ was defined as the suggestive significant threshold. Subsequently, associations reaching the multiple corrected significant level were further
validated by three robust MR methods, including MR-PRESSO\textsuperscript{[44]}, weighted median (WM)\textsuperscript{[45]} and MR-Egger\textsuperscript{[46]}, to obtained more reliable results. Consistently, FDR correction was also conducted with N equal to the number of the included associations. We defined the association showing FDR < 0.05 in at least 2 validation methods as robust causal relationships, and association showing FDR < 0.05 in only 1 method as potential causal relationships.

As sensitivity analyses, the Cochran's Q test was applied to detect heterogeneity and the MR-Egger intercept test was used to identify horizontal pleiotropic effects. Single SNP analyses and leave-one-out analyses were also adopted to provide visualization of the MR results. F-statistic for IVs were calculated to identify weak instrument (F<10). Moreover, Mrlap was conducted as additional sensitivity analyses between sleep characteristics and hand OA, to avoid potential bias of sample overlap\textsuperscript{[47]}.

All analyses were conducted using R software (version 4.1.0) with the following packages: ‘TwoSampleMR’, ‘MR-PRESSO’, and ‘Mrlap’ ( https://github.com/n-mounier/MRlap ). Statistical tests were two-sided, and P values below 0.05 were considered indicative of statistically significant differences.

Result

Baseline characteristics

In the observational analysis, a total of 387,822 participants were included (Table 1). Among them, 296,672 participants had complete genetic information (eTable 4 in the Supplement 1). Participants lacking complete sleep information, those lost to follow-up, or those with a history of degenerative skeletal disorders diagnosis before baseline were excluded. Within the cohort, women were found to have higher sleep scores compared to men. Those with poorer sleep scores had a higher incidence obesity, diabetes, and hypertension. In contrast, participants with higher sleep scores were more likely to adopt a healthy lifestyle, characterized by consuming more vegetables, fruits, and minerals, demonstrating higher physical activity participation, and having a lower percentage of smokers or alcohol drinkers.

Observational analysis

Sleep pattern and genetic risks: Multivariable Cox regression analysis revealed an inverse association between sleep score and the risk of degenerative skeletal disorders (Figure 2). Individuals with a sleep score of 5 demonstrated approximately a 38% lower risk of overall degenerative skeletal disorders compared to those with a sleep score of 0-1 (Hazard Ratio [HR]: 0.62, 95% Confidence Interval [CI]: 0.59-0.65). Notably, a more pronounced risk reduction was observed for spinal degeneration, with HR (95% CI) of 0.36 (0.28-0.46) for CDD, 0.49 (0.44-0.56) for LDD, and 0.43 (0.39-0.47) for spondylosis. In addition, replication results of diagnostic sleep also showed that sleep disorders were strongly associated with an increased risk of degenerative bone disorders (eTable 5 in the Supplement 1).
When considering the genetic risk of degenerative bone disease, we found that PRS is synergistic with sleep (eTable 6 in the Supplement 1). Compared with individuals with healthy sleep patterns and lower genetic risk, individuals with poor sleep and higher genetic risk had up to 46%, 169%, 5%, 48%, 190%, 129%, 120% and 79% higher risk of overall OA, hand OA, hip OA, knee OA, CDD, LDD, Spondylosis and OP respectively (eFigure 1 in the Supplement 1).

**Sleep characteristics and degenerative skeletal disorders**

Analysis of specific sleep characteristics indicated that insomnia and short sleep duration were associated with an increased risk of all degenerative skeletal disorders (Figure 3). Although long sleep duration was not statistically significantly associated with OA, it was associated with increased risk of spinal degeneration and OP. The association between early chronotype and degenerative skeletal disorders showed complexity, with positive correlation with peripheral joint degeneration, negative correlation with spinal degeneration, and no significant correlation with OP. Daytime sleepiness was associated with an increased risk of degenerative skeletal disorders, except for hand OA. Snoring demonstrated a weak association with overall OA and knee OA, with no clear correlation with other degenerative skeletal disorders (Figure 3).

**Bidirectional two-sample MR analyses**

IVs in the first stage of MR analyses were available in supplementary data (Supplement 2). The selected IVs could explain 0.14%-2.79% of the variance of corresponding sleep exposures. The IVs were less likely to be weak instruments since all F statistics were above 10 (28-209) (Supplement 3).

**Causal effects of sleep characteristics on degenerative skeletal disorders**

Under an overall scan by IVW, 8 associations between sleep characteristics and degenerative skeletal disorders have reached the multiple-testing significant levels and 6 associations were suggestive significant (Figure 3). In the following validation stage, 4 pairs of causal associations were found to be robust, which identified by both MR-PRESSO and WM: (1) short sleep duration and overall OA (OR=2.88, 95%CI: 1.63-5.07, FDR<0.01), (2) short sleep duration and knee OA (OR=2.50, 95%: 1.33-4.68, FDR=0.01), (3) short sleep duration and LDD (OR=2.97, 95%CI: 1.63-5.41, FDR<0.01), (4) long sleep duration and LDD (OR=0.13, 95%CI: 0.03-0.53, FDR=0.02) (Figure 4). Meanwhile, 4 potential causal relationships were only identified by MR-PRESSO: (1) Insomnia and LDD (OR=1.25, 95%CI: 1.07-1.14, FDR=0.02), (2) insomnia and spondylosis (OR=1.31, 95%CI: 1.11-1.55, FDR=0.01), (3) early chronotype and overall OA (OR=1.09, 95%CI. 1.02-1.16, FDR=0.02), (4) short sleep duration and CDD (OR=5.41, 95%CI: 1.95-15.01, FDR<0.01) (eTable 7 in the Supplement 1).

Heterogeneity were founded in the tests of early chronotype, short sleep duration and overall OA , as well as short sleep duration and knee OA, LDD (P<0.05) (eTable 8 in the Supplement 1). However, considering that both of the two robust methods, MR-PRESSO and WM, provided consistent effect directions, these results were less likely to be caused by accidental errors. Pleiotropic effects haven't been detected in any
test(eTable 8 in the Supplement 1). Moreover, the leave-one analysis showed that the main results were not driven by a single genetic variation (eFigure 2 in the Supplement 1). Otherwise, Mrlap showed that impact of sample overlap between sleep characteristics and hand OA was mild (eTable 9 in the Supplement 1). Results of other sensitivity analyses were available in supplemental material. (eFigure 3-5 in the Supplement 1).

**Reverse MR analyses**

In the reverse MR analysis, we explored the causal effect of degenerative skeletal disorders on sleep. The IVW showed no significant association between 8 degenerative skeletal disorders and 6 sleep characteristics (eFigure 6 in the Supplement 1).

**Discussion**

In this study, we investigated the association between sleep and degenerative skeletal disorders risk using 2 approaches. Findings from the UK Biobank prospective cohort study showed that poor sleep is associated with an increased risk of degenerative skeletal disorders. 37 pairs of associations were found between 6 sleep characteristics and 8 degenerative skeletal diseases. Furthermore, the synergistic effect of PRS with sleep patterns confirms that degenerative skeletal disorders received both genetic and lifestyle effects. MR analyses further identified that 8 of these pairs of associations had causal effects. Among these, insomnia and sleep duration had the most significant effect on degenerative skeletal disorders, especially in the spine, which is similar to the trend in observational studies. Our findings provide solid evidence for an association between sleep and degenerative skeletal disorders.

**Comparison with other studies**

Previous studies focused on the effects of frequent insomnia, sleep disorders and short sleep duration on skeletal degeneration. Several large population-based observational and follow-up studies over the past decades have confirmed that insomnia and short sleep duration are significantly associated with increased risk of OA and OP\(^{[23, 26, 48-51]}\). However, no observational studies have reported associations between sleep characteristics and spinal degeneration. Our prospective cohort study found that insomnia and short sleep duration were associated with an increased risk of all degenerative skeletal phenotypes. Genetic risk assessment has reaffirmed that the development of degenerative skeletal disorders is influenced by both innate genetics and acquired lifestyle\(^{[14]}\).

In inferring causality, Ni et al. reported, based on MR analysis, insomnia and short sleep duration both had an unfavorable causal effect on overall OA\(^{[25]}\). Liu et al. showed that insomnia and short sleep duration were significantly and causally associated with increased risk of CDD and LDD in their MR study\(^{[52]}\). Another MR investigation, delving into the broader impact of insomnia on various health outcomes, identified genetically predicted insomnia as causally associated with an elevated risk of spondylosis\(^{[53]}\). In our MR analyses, unfavorable causal associations were observed for insomnia on LDD
and spondylosis, as well as for short sleep duration on overall OA, knee OA, CDD, and LDD. Differences between the results of the studies may stem from variations in IVs and population selection. Furthermore, consistent with previous studies, although observational studies established an association between insomnia and short sleep duration and OP risk, MR studies did not support the causality of this association\[54\]. Although the association between long sleep duration and LDD is contradictory in observational study and MR analysis, considering that the former is more likely to be influenced by confounders, we believe that MR-suggested associations deserve more attention. Finally, although previous studies have reported a possible interaction between sleep disorders and OA, our study did not find any inverse association\[55\].

The association between sleep and the risk of degenerative skeletal disorders might be explained by a few potential factors. Studies have shown that melatonin regulates bone metabolism and inhibits cartilage apoptosis, and its deficiency can lead to joint degeneration\[56-58\]. The effects of sleep on melatonin secretion is a potential biological mechanisms\[59\]. This mechanism could explain why insomnia, short sleep duration, and early chronotype have the greatest impact on skeletal degeneration, rather than snoring or daytime sleepiness, as sleep deprivation and circadian rhythms have the most significant impact on melatonin secretion\[59\]. Moreover, the burst of inflammation triggered by sleep deprivation could be another potential mechanism\[60\]. The effect of inflammation on skeletal degeneration has been confirmed by numerous studies\[61,62\]. Future research addressing these mechanisms is clearly necessary.

**Strength and Limitations**

The present study provided a comprehensive assessment of the association between sleep and degenerative skeletal disorders. Our results provide support for previously established evidence as well as a preliminary report of unknown associations. The main strength of this study is the use of both observational and MR analyses to assess the association between sleep and degenerative skeletal disorders. the UK Biobank provided a large amount of participant data for the observational study, whilst the multiple MR analysis methods ensured the robustness of the results. However, potential limitations are hard to avoid. First, the presence of a “healthy volunteers” bias in the UK Biobank dataset may have influenced our observations. Second, the sleep information collected from the baseline questionnaire may reflect only the participant’s sleep status at a particular point in time. However, we also used diagnostic sleep disorders for repeated analyses to avoid bias in questionnaire information as much as possible. Third, observational studies make it difficult to make causal inferences about associations and to rule out potential reverse associations. Thus, we also use reverse MR analysis to discover possible reverse associations. Fourth, since MR method was sometimes conservative, some significant associations may be obscured by multiple correction in our framework of multi-exposure and multi-outcome tests. For this reason, we also used multiple methods to identify each potential causal estimate. Finally, our observational and MR study was restricted to European sample, thus it should be cautious to extent our results to other populations.
Conclusion

In conclusions, this study established a significant association between sleep and the risk of degenerative skeletal disorders. Our results suggested that sleep deprivation or circadian rhythm disturbances including insomnia, short sleep duration and early chronotype can exacerbate joint degeneration. Although the underlying mechanisms need to be further investigated, prioritizing strategies to enhance sleep quality, prevent insomnia, and maintain optimal sleep duration becomes crucial for delaying the onset of skeletal degeneration.

Abbreviations

GWAS  Genome-wide association studies
IVW   Inverse-variance weighted
MR    Mendelian Randomization
OA    Osteoarthritis
IDD   Intervertebral disc degeneration
CDD   Cervical disk disorders
LDD   Lumbar disk disorders
OP    Osteoporosis
UKB   UK Biobank
PRS   Polygenic risk scores
HDL   High-density lipoprotein
SD    Standard Deviation
IVs   Instrument variables
SNPs  Single-nucleotide polymorphisms
FDR   False discovery rate
WM    Weighted median
CI    Confidence Interval
HR    Hazard Ratio
Declarations

Acknowledgements

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Conflict of interest: The authors declared that no competing interests exist.

Data accessibility: UK Biobank is an open-access resource, and the study website https://www.ukbiobank.ac.uk/ has information on available data and access procedures.

Data sets used for the analysis will be made available under reasonable requests.

Ethics statement: This study was approved by the North West Multi-center Research Ethics Committee, the England and Wales Patient Information Advisory Group, and the Scottish Community Health Index Advisory Group (application number 51671, 71986). All participants provided written informed consent prior to data collection.

Consent for publication:

Not applicable.

References


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**Tables**

**Table 1.** Baseline characteristics according to healthy sleep score.
### Healthy Sleep Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>0-1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>Participants, n</td>
<td>387822</td>
<td>9028</td>
<td>42896</td>
<td>108595</td>
<td>143424</td>
<td>83879</td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>56.78 (8.09)</td>
<td>56.87 (7.71)</td>
<td>57.02 (7.84)</td>
<td>56.99 (7.97)</td>
<td>56.70 (8.15)</td>
<td>56.49 (8.30)</td>
</tr>
<tr>
<td>Sex, Male, (n%)</td>
<td>174507 (45.0)</td>
<td>4457 (49.4)</td>
<td>20447 (47.7)</td>
<td>52641 (48.5)</td>
<td>65951 (46.0)</td>
<td>31011 (37.0)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>368348 (95.0)</td>
<td>8384 (92.9)</td>
<td>40537 (94.5)</td>
<td>103052 (94.9)</td>
<td>136399 (95.1)</td>
<td>79976 (95.3)</td>
</tr>
<tr>
<td>Mean IDM (SD)</td>
<td>16.76 (13.68)</td>
<td>20.76 (15.94)</td>
<td>18.54 (14.73)</td>
<td>17.29 (14.03)</td>
<td>16.23 (13.25)</td>
<td>15.67 (12.93)</td>
</tr>
<tr>
<td>Obesity, Yes (%)</td>
<td>137405 (35.5)</td>
<td>4992 (55.6)</td>
<td>19784 (46.3)</td>
<td>42764 (39.5)</td>
<td>47718 (33.4)</td>
<td>22147 (26.5)</td>
</tr>
<tr>
<td>Mean TG(SD), mmol/L</td>
<td>1.74 (1.02)</td>
<td>2.05 (1.21)</td>
<td>1.90 (1.10)</td>
<td>1.80 (1.06)</td>
<td>1.71 (1.00)</td>
<td>1.58 (0.91)</td>
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<tr>
<td>Mean HDL(SD), mmol/L</td>
<td>1.45 (0.38)</td>
<td>1.35 (0.36)</td>
<td>1.40 (0.38)</td>
<td>1.43 (0.38)</td>
<td>1.46 (0.38)</td>
<td>1.51 (0.39)</td>
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<tr>
<td>Diabetes, n(%)</td>
<td>66373 (19.6)</td>
<td>2443 (30.6)</td>
<td>9175 (24.3)</td>
<td>19762 (20.8)</td>
<td>23102 (18.4)</td>
<td>11891 (16.3)</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>281491 (72.7)</td>
<td>7075 (78.5)</td>
<td>32669 (76.3)</td>
<td>80868 (74.6)</td>
<td>103368 (72.1)</td>
<td>57511 (68.6)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current</td>
<td>40198 (10.4)</td>
<td>1632 (18.1)</td>
<td>6350 (14.8)</td>
<td>13131 (12.1)</td>
<td>13497 (9.4)</td>
<td>5588 (6.7)</td>
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<td>Never</td>
<td>213351 (55.0)</td>
<td>3900 (43.2)</td>
<td>20236 (47.2)</td>
<td>56098 (51.7)</td>
<td>80626 (56.2)</td>
<td>52491 (62.6)</td>
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<td>Previous</td>
<td>134273 (34.6)</td>
<td>3496 (38.7)</td>
<td>16310 (38.0)</td>
<td>39366 (36.3)</td>
<td>49301 (34.4)</td>
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</tr>
<tr>
<td>Drinking (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>80870 (20.9)</td>
<td>1934 (21.4)</td>
<td>9508 (22.2)</td>
<td>23944 (22.0)</td>
<td>30224 (21.1)</td>
<td>15260 (18.2)</td>
</tr>
<tr>
<td>1-4 times a week</td>
<td>192936 (49.7)</td>
<td>3922 (43.4)</td>
<td>20005 (46.6)</td>
<td>53269 (49.1)</td>
<td>72760 (50.7)</td>
<td>42980 (51.2)</td>
</tr>
<tr>
<td>1-3 times a month</td>
<td>42696 (11.0)</td>
<td>1074 (11.9)</td>
<td>4798 (11.2)</td>
<td>11787 (10.9)</td>
<td>15379 (10.7)</td>
<td>9658 (11.5)</td>
</tr>
<tr>
<td>Special occasions only/Never</td>
<td>71320 (18.4)</td>
<td>2098 (23.2)</td>
<td>8585 (20.0)</td>
<td>19595 (18.0)</td>
<td>25061 (17.5)</td>
<td>15981 (19.1)</td>
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<td></td>
<td>147699 (38.1)</td>
<td>2913 (32.3)</td>
<td>14743 (34.4)</td>
<td>38820 (35.7)</td>
<td>55121 (38.4)</td>
<td>36102 (43.0)</td>
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<tr>
<td>Fruits&amp;Vegetables ≥ 5 portion, n(%)</td>
<td>147699 (38.1)</td>
<td>2913 (32.3)</td>
<td>14743 (34.4)</td>
<td>38820 (35.7)</td>
<td>55121 (38.4)</td>
<td>36102 (43.0)</td>
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<tr>
<td>Vitamin intake, n(%)</td>
<td>58621 (15.1)</td>
<td>1509 (16.7)</td>
<td>6607 (15.4)</td>
<td>16384 (15.1)</td>
<td>21338 (14.9)</td>
<td>12783 (15.2)</td>
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<td>Mineral intake, n(%)</td>
<td>84219 (21.7)</td>
<td>1849 (20.5)</td>
<td>9139 (21.3)</td>
<td>23271 (21.4)</td>
<td>31091 (21.7)</td>
<td>18869 (22.5)</td>
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<tr>
<td>Mean MET (SD)</td>
<td>24.40 (31.54)</td>
<td>21.01 (31.85)</td>
<td>21.98 (31.15)</td>
<td>23.56 (31.40)</td>
<td>24.82 (31.44)</td>
<td>26.38 (31.89)</td>
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<tr>
<td>Sleep duration (SD)</td>
<td>7.17 (1.08)</td>
<td>6.46 (1.77)</td>
<td>6.64 (1.52)</td>
<td>7.00 (1.25)</td>
<td>7.34 (0.85)</td>
<td>7.46 (0.50)</td>
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Figures

Figure 1

Schematic diagrams illustrating the study designs and the three key assumptions.

(A). Observational study in the UK Biobank (UKB) adjusted for potential confounders.

(B). Principles of Mendelian randomization and assumptions. Assumption : genetic variants are strongly associated with the exposure; Assumption : genetic variants are not associated with confounders;
Assumption: genetic variants are not associated with the outcome by pathways or phenotypes other than the exposure.

Figure 2

Associations between sleep score and degenerative skeletal disorders.
Figure 3

Observational and Two-sample MR estimates for the association of sleep characteristics with degenerative skeletal disorders.

*Statistically significant causal associations observed by the inverse variance weighting (IVW) method.

**Causal associations that remain robustly significant after correction for multiple testing (FDR < 0.05).
<table>
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<th>Exposure</th>
<th>Outcome</th>
<th>Methods</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>FDR</th>
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<td>Insomnia</td>
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<td>MR-PRESSO</td>
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<td>&lt; 0.01</td>
<td>1.38E-02</td>
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<td>9.88E-01</td>
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<td>LDD</td>
<td>MR-PRESSO</td>
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<td>Overall OA</td>
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<td>1.54E-02</td>
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<td></td>
<td>0.99</td>
<td>9.88E-01</td>
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<td>Weighted median</td>
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</tbody>
</table>

**Figure 4**

Sensitivity analysis for significant sleep characteristics on degenerative skeletal disorders passing Multiple test.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement1.docx
- supplement2.xlsx
- supplement3.xlsx