Association Between Bone Mineral Density, Sleep Disturbance and Sleep Duration: Results from Observational and Mendelian randomization study

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Research Article

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Abstract

Purpose

The relationship between bone health and sleep problems still remains controversial across different study conditions. This study aims to investigate the association between sleep disturbance, sleep duration and bone mineral density(BMD) using observational and Mendelian randomization(MR) study.

Methods

A total of 6,421 participants from the National Health and Nutrition Examination Survey (NHANES) 2007–2010 were included in this study. The association between sleep disturbance, sleep duration, and BMD was assessed using multivariable linear regression analysis. Two-sample MR analysis was employed to corroborate the observational study results. Five methods were utilized to estimate causal effects, with the primary approach being the inverse variance-weighted (IVW) analysis.

Results

Sleep disturbance exhibited a negative association with BMD in both the femoral neck (β: -0.03; 95% CI, -0.04 to -0.02), and lumbar spine (β: -0.01; 95% CI, -0.02 to 0.00). This association remained significant after adjusting for known confounders, with β values of -0.01 (95% CI, -0.02 to -0.01) for the femoral neck and − 0.01 (95% CI, -0.02 to 0.00) for the lumbar spine. No significant association was observed between sleep duration and BMD, and stratification analysis by sleep disturbance yielded similar results. MR analysis appeared to indicate a consistent trend in the causal association between sleep disorder and BMD at the femoral neck using IVW methods (β: -0.039; 95% CI: -0.142 to 0.063), and lumbar spine(β: -0.041; 95% CI: -0.182 to 0.101), and the other 4 methods showed consistent results, although no significant difference was observed. There was no statistical difference found in the MR analysis for the causal relationship between BMD and sleep duration.

Conclusions

The study suggests potential causal associations between sleep disorders and a higher risk of bone loss. Additionally, there is no evidence to indicate that extending sleep duration could compensate for bone loss caused by sleep disorders.

Introduction

Osteoporosis is indeed a common disease characterized by reduced bone mineral density (BMD) and an increased risk of fracture. Each year, there are over 8.9 million fracture cases worldwide, with an osteoporotic fracture occurring approximately every three seconds[1]. This trend is exacerbated by the

aging population, leading to a surge in the number of osteoporosis patients[2]. Historically, osteoporosis was considered a chronic condition affecting older and post-menopausal women[3], and recent studies have shown that osteoporosis or osteopenia is also prevalent among younger adults, specifically those aged 20–39[4]. Fractures resulting from osteoporosis, such as hip and vertebral fractures, can lead to various complications, including kyphosis, restrictive lung disease, and psychological problems[1]. Therefore, it is crucial to focus on improving treatment and prevention strategies based on the etiology of the disease. Risk factors of bone loss include alcohol drinking[5], smoking[6], and diabetes[7]. Recently,emerging research has highlighted the significant role of lifestyle factors, beyond traditional risk factors ,lifestyle factors (such as sleep disorders) may also contribute to play a significant role in osteoporosis.

Sleep problems can manifest as sleep disturbances and excessive or inadequate sleep, and their role in decreasing bone mass remains controversial. Some studies have observed a correlation between low bone mineral density (BMD) and either short or prolonged sleep duration[8,9], while others have found no associations[10,11]. Sleep disturbance has been established as a risk factor linked to chronic diseases[12,13]. However, a prospective cohort study conducted by Pan et al. found no significant association between sleep disturbance and BMD at any skeletal sites[14]. This finding may contradict our current perspectives and previous literature, which have indicated that sleep disruption can trigger inflammation, reduce growth hormone levels, and ultimately lead to bone loss[15–17]. Furthermore, it is noteworthy that individuals commonly attempt to compensate for sleep disturbances by increasing their sleep duration in hopes of mitigating potential health damage. An evaluation of the sleep habits of adults in the US highlighted a significant discrepancy in sleep duration between workdays and days off, as well as a high prevalence of sleep disturbance[18]. These findings emphasize the need for further investigation into the effects of both sleep disturbance and duration on overall health outcomes.

Randomized controlled trials (RCTs) are considered a valuable method for establishing a causal association between sleep health and BMD providing higher quality evidence. However, RCTs have limitations that restrict their use in clinical settings, such as higher costs and ethical considerations. In contrast, Mendelian randomization (MR) studies utilize genetic variants, known as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to examine the causal relationship between potential risk factors and outcomes[19]. Unlike traditional observational studies, MR studies are less susceptible to be confounded by other factors because the allocation of SNPs occurs randomly during gamete formation and is not influenced by socioeconomic or health status[20]. Furthermore, the increasing number of genome-wide association studies (GWAS) in recent years has explored the genetic associations between sleep duration, sleep disorders, and BMD. Therefore, in this study, our aim is to utilize the National Health and Nutrition Examination Survey (NHANES) database to investigate the effects of sleep quality on BMD. Subsequently, we verify these findings through two-sample MR analysis, using available SNPs associated with sleep quality and BMD. This approach will provide a higher quality of evidence for the impact of sleep habits on bone health.

Methods

Data Source and Study Population

The NHANES program, conducted by the National Centers for Disease Control and Prevention, is a robust survey that collects data from a representative sample of noninstitutionalized civilians in the US. The survey is carried out in 2-year cycles using stratified, multistage, and random methodologies to ensure the accuracy of the data. To gather the required information, NHANES employs various methods including household interviews, physical examinations, and blood tests conducted at mobile examination centers (MECs). For this particular study, a cross-sectional analysis was conducted using data from two NHANES survey cycles, specifically the years 2007–2008 and 2009–2010. The study focused on adult participants aged 20 years and older, resulting in a total of 6,421 individuals meeting the inclusion criteria(Fig. 1). Prior to their participation in the survey, all included participants provided written informed consent. As the NHANES survey and its data are reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS), and the data are publicly accessible, the current analysis was exempted from the need for additional institutional review and approval.

Outcome Variables

The BMD (g/cm^2) of the femoral neck and the lumbar spine (the average of L1 to L4) were measured using dual-energy x-ray absorptiometry (DXA). Detail information about the BMD examination can be found on previous reports[21].

Exposures Variables

Sleep disturbance was evaluated with the questionnaire: “Have you ever told a doctor or other health professional that you have trouble sleeping?” The answer categories were “Yes,” “No,” “Refused,” and “Do not know.” The data would be considered as missing value if the answer was “Refused,” or “Do not know.” Sleep duration was evaluated by the question: “How much sleep do you usually get at night on weekdays or workdays?” The answer categories range 1–11, with 12 meaning the sleep duration ≥ 12 h. Based on the recommendations of the National Sleep Foundation[22], sleep duration was divided into three categories: insufficient (< 7 h/day) adequate (7 ~ 9 h/day), and excessive (> 9 h/day).

Covariates

The covariates of our study included gender, age, ethnicity, education, poverty to income ratio, health insurance, smoking, alcohol drinking, body mass index (BMI), diabetes and hypertension. Both age and BMI were treated as continuous variables. And the categories of other covariates were described as follows: gender (male or female), ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American,

or other), education (College graduate or above, Some College, High school or below), poverty to income ratio (≤ 130%, 131–338%, and ≥ 339%), health insurance, smoking, alcohol drinking, diabetes (defined as a clinical diagnosis of diabetes or elevated levels of fasting glucose (≥ 7.0 mmol/L), HbA1c (≥ 6.5%), or non-fasting glucose (≥ 11.1 mmol/L)), and hypertension (defined as a clinical diagnosis of hypertension or having systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg). Physical activity was collected from the Global Physical Activity Questionnaire, and divided into physical active and inactive groups according to whether the PA guidelines of 2018 was met[23]. The formula for calculating the physical activity can be found in previous studies[24,25].

Statistical analysis

Weighted analysis was employed in all analyses to account for the representativeness of the NHANES database for the entire noninstitutionalized civilian population of the US. To compare the baseline characteristics between the sleep disturbance and non-sleep disturbance groups, t-tests were used for continuous variables, while chi-square tests were used for categorical variables. To examine the relationship between bone mineral density (BMD), sleep disturbance, and sleep duration, multivariate generalized linear regression was utilized, with β-value and 95% confidence intervals (CI) calculated, adjusting for matching variables in different models, including crude model (no confounders adjusted), model 1 (age, gender, ethnicity) and model 2 (further adjusted for poverty to income ratio, insurance coverage, education, smoking, alcohol drinking, hypertension, diabetes and BMI). To evaluated the effect of sleep duration on the sleep disturbance regarding of BMD, subgroup analysis based on sleep disturbance was conducted.

Mendelian randomization

Data resources for exposure genetic variants

The SNPs associated with sleep duration were obtained from a large-scale GWAS study conducted on the UK Biobank dataset. This study identified a total of 78 SNPs associated with continuous sleep duration, as well as 27 SNPs associated with short sleep duration (< 7 hours) and 8 SNPs associated with long sleep duration (> 8 hours)[26]. For sleep disorder, SNPs were extracted from Finngen database (https://finngen.gitbook.io/documentation/), which collected data from 377,277 individuals. In Finngen database, GWAS data are imputed using the Finnish population-specific SISu v4 reference panel. According to Finngen (https://risteys.finngen.fi), the sleep disorder is a combination of insomnia, hypersomnia, disorder of the sleep-wake schedule, sleep terrors, nightmares and other sleep disorders.

Data resources for outcome genetic variants

In order to align with the variables of the observational study, we selected the SNPs associated with BMD of femoral neck and lumbar spine from a large GWAS meta-analysis conducted by the GEnetic Factors for OSteoporosis (GEFOS) Consortium. This consortium included 53,236 participants of

European ancestry[27]. The BMD of femoral neck and lumbar spine(L1-L4) was measured through DXA. Each single variant with a minor allele frequency (MAF) > 0.5% was tested for its effect on BMD, adjusting for sex, age, age^2, weight and standardized to have a mean of zero and a standard deviation of one. This standardization method helps to minimize any potential bias caused by variations in the measuring machine used.(Table S1)

Selection of SNPs for MR analysis

To ensure the quality of the selected SNPs, several control steps were taken. Firstly, SNPs associated with exposure variants needed to be genome-wide significant ($P < 5\times10^{-8}$). Secondly, instrumental SNPs for the exposure in linkage disequilibrium (LD) could lead to biased outcomes. Therefore, we conducted the clumping process with $R^2 < 0.001$ and window size = 10,000 kb based on the LD reference panel of the European 1000 genomes project[28], and those SNPs absent from the LD reference panel were removed. Thirdly, SNPs with a minor allele frequency (MAF) below 0.01 were also eliminated. Fourthly, the SNPs of exposure variants would be removed if they were not retrieved in the outcome variants. Fifthly, harmonization process were performed to align the ambiguous (e.g., A/G vs. A/C) or palindromic SNPs (with A/T or G/C pairs), with some possible SNPs excluded from the previous selected SNPs. The SNPs of long sleep duration were too limited to test its effects and thus were excluded in MR analysis. Finally, the number of selected SNPs for continuous sleep duration, short sleep duration and sleep disorder was 56, 18 and 13 respectively, and the detailed information was listed in Table S2.

MR analysis and sensitivity analysis

In the present study, a two-sample Mendelian randomization (MR) analysis was conducted to investigate the causal effects of continuous sleep duration, short sleep duration, and sleep disorder on BMD at the femoral neck and lumbar spine. Several different MR methods were used, including the inverse variance weighted (IVW) under a random-effects model, MR-Egger, weighted median, simple mode, and weighted mode methods. Among these, IVW was considered the primary method as it incorporates the Wald ratios of each SNP's causal effect through meta-analysis, leading to more accurate estimates[29]. A consistent effect trend across these approaches would strengthen the evidence for a causal relationship. To address potential biases introduced by pleiotropic instrumental variables (IVs), sensitivity analysis was performed. Heterogeneity was quantified using Cochran's Q statistic, where a significance level of $p < 0.05$ indicated significant heterogeneity. The MR-Egger intercept was used to assess the possibility of horizontal pleiotropy, with a significance level of $p < 0.05$ indicative of potential horizontal pleiotropy. Additionally, the MR-PRESSO method was employed to detect outliers when horizontal pleiotropy was observed. In the sensitivity analysis for the association between continuous sleep duration and BMD at the lumbar spine, significant heterogeneity was detected ($p = 0.017$), and the potential outlier SNP rs1991556 was identified using MR-PRESSO analysis. Consequently, this SNP was excluded from further MR analysis. Furthermore, a leave-one-out analysis was conducted to examine whether specific variants had a substantial impact on the results.

All analyses were performed using R (version 4.2.3, http://www.R-project.org, The R Foundation), and the R package “TwoSampleMR” was used for MR analysis. P-value less than 0.05 was considered statistically significant.

Results

Population characteristics

The baseline characteristics of study participants are summarized in Table 1. Among the 6421 participants included in the study, the mean age was 42.9 ± 0.3 and 47.1 ± 0.4 years in the control and case groups, respectively ($p < 0.0001$). A significant gender difference was noted, with a higher prevalence of females in the group with sleep disturbance, whereas males predominated in the group without sleep disturbance. Compared to the case group, the control group exhibited higher BMD in both the femoral neck (0.856 ± 0.003 VS 0.821 ± 0.004, $p < 0.0001$) and lumbar spine (1.040 ± 0.003 VS 1.026 ± 0.004, $p = 0.013$). Regarding sleep duration, participants with sleep disturbance reported less adequate sleep compared to the control group, resulting in an inclination to prolong their sleep duration. Similarly, a higher percentage of individuals in the control group were observed to be physically active. Statistical differences were also noted in ethnicity, insurance coverage, smoking, alcohol consumption, BMI, hypertension, and diabetes status($p < 0.05$).

Table 1
The baseline characteristics of the participants by the sleep disturbance status.

Characteristics	Non Sleep Disturbance	Sleep Disturbance	P value
BMD			
Femoral neck	0.856 ± 0.003	0.821 ± 0.004	**< 0.0001**
Lumbar spine	1.040 ± 0.003	1.026 ± 0.004	**0.013**
Sleep duration			**< 0.0001**
insufficient	32.50(1.04)	49.59(1.95)	
enough	65.79(1.12)	48.34(1.87)	
excessive	1.71(0.21)	2.07(0.47)	
Physical active	69.5(1.0)	65.2(1.6)	**0.02**
Age	42.9 ± 0.3	47.1 ± 0.4	**< 0.0001**
Gender			**< 0.0001**
Male	53.0(0.9)	40.1(2.0)	
Female	47.0(0.9)	59.9(2.0)	
Ethnicity			**< 0.0001**
Non-Hispanic White	67.1(2.5)	78.9(2.3)	
Non-Hispanic Black	10.8(1.0)	9.2(1.0)	
Mexican American	10.0(1.4)	4.6(1.1)	
other	12.1(1.3)	7.3(1.0)	
Education background			0.1
College graduate or above	29.1(1.5)	27.2(1.7)	
Some College	29.7(0.7)	32.8(1.3)	
High school or below	41.2(1.7)	40.0(2.2)	
Poverty to income ratio			0.4
<=130%	20.1(1.1)	20.5(1.6)	
131–338%	32.6(1.2)	30.5(1.7)	
>=339%	47.3(1.6)	49.0(2.3)	

Data are presented as mean ± standard error for continuous variables and percentage (standard error) for categorical variables. P-value was calculated by the weighted t-test for continuous variables and the chi-square test for categorical variables. BMI: body mass index.

Characteristics	Non Sleep Disturbance	Sleep Disturbance	P value
BMD			
Health insurance	77.0(1.1)	85.9(1.2)	**< 0.0001**
Smoking	42.5(1.5)	53.0(1.6)	**< 0.0001**
Alcohol drinking	89.6(0.6)	92.1(0.9)	**0.04**
BMI	27.54 ± 0.12	28.28 ± 0.15	**< 0.001**
Hypertension	27.1(1.1)	39.9(1.0)	**< 0.0001**
Diabetes	9.2(0.6)	13.7(1.0)	**< 0.0001**

Data are presented as mean ± standard error for continuous variables and percentage (standard error) for categorical variables. P-value was calculated by the weighted t-test for continuous variables and the chi-square test for categorical variables. BMI: body mass index.

Association between sleep disturbance, sleep duration and BMD

Sleep disturbance demonstrated a negative association with BMD in both the femoral neck (β: -0.03; 95% CI, -0.04 - -0.02), and lumbar spine (β: -0.01; 95% CI, -0.02–0.00), as illustrated in Table 2. Even after adjusting for known confounders, this association remained statistically significant, with values of (β: -0.01; 95% CI, -0.02 - -0.01) for femoral neck and (β: -0.01; 95% CI, -0.02–0.00) for lumbar spine. Surprisingly, no significant differences were observed between sleep duration and BMD, whether in the femoral neck or lumbar spine, when adjusting for confounders. Subsequently, when we stratified the subjects based on sleep disturbance status to explore the impact of sleep duration, no significant differences were observed among them($p > 0.05$), as depicted in Table 3. To further elucidate the effects of sleep duration, we presented the distribution of BMD in the femoral neck and lumbar spine in subjects with sleep disturbance by sleep duration (Fig. 2), which aligns with the aforementioned results.

Table 2
The association between sleep disturbance, sleep duration and BMD in femoral neck and lumbar spine.

	Crude model		**Model 1**		**Model 2**	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Femoral neck						
Sleep disturbance						
no	Reference		Reference		Reference	
yes	**-0.03(-0.04,-0.02)**	**< 0.0001**	**-0.01(-0.02,0.00)**	**0.03**	**-0.02(-0.02,-0.01)**	**0.001**
Lumbar spine						
Sleep disturbance						
no	Reference		Reference		Reference	
yes	**-0.01(-0.02,0.00)**	**0.01**	-0.01(-0.02,0.00)	0.24	**-0.01(-0.02, 0.00)**	**0.03**
Femoral neck						
Sleep duration						
adequate	Reference		Reference		Reference	
insufficient	**0.01(0.00,0.02)**	**0.02**	0(-0.01,0.01)	0.49	-0.01(-0.01, 0.00)	0.22
excessive	-0.01(-0.05,0.03)	0.57	-0.01(-0.04,0.02)	0.46	0(-0.03, 0.03)	0.97
Lumbar spine						
Sleep duration						
adequate	Reference		Reference		Reference	
insufficient	0(0.00,0.01)	0.29	0(-0.01,0.01)	0.82	-0.01(-0.02, 0.00)	0.10
excessive	0.01(-0.02,0.05)	0.50	0.01(-0.03,0.05)	0.60	0.02(-0.02, 0.06)	0.29

Crude Model: no covariate adjusted; Model 1: adjusted for age, sex, ethnicity; Model 2: further adjusted for poverty to income ratio, insurance coverage, education, smoking, alcohol drinking, hypertension, diabetes, BMI, physical activity.

Table 3
The association between sleep duration and BMD stratified by sleep disturbance status.

	Sleep duration				
	adequate	insufficient	P-value	excessive	P-value
Femoral neck					
Sleep disturbance					
yes	Ref.	0(-0.01,0.02)	0.58	0.05(-0.05,0.14)	0.31
no	Ref.	0(-0.01,0.01)	0.39	-0.01(-0.04,0.02)	0.44
Lumbar spine					
Sleep disturbance					
yes	Ref.	0(-0.02,0.02)	0.97	0.07(-0.02,0.15)	0.10
no	Ref.	-0.01(-0.02, 0.00)	0.18	0(-0.03, 0.03)	0.82
Adjusted for age, sex, ethnicity, poverty to income ratio, insurance coverage, education, smoking, alcohol drinking, hypertension, diabetes, BMI, physical activity.					

Table 4
The results of IVW in MR analysis.

Exposure	outcome	N of SNPs	β	95% CI	P Value	QP value	MR Egger-intercept	MR Egger-intercept-P value
Sleep disorder	FN-BMD	13	-0.039	(-0.142, 0.063)	0.449	0.641	0.001	0.950
	LS-BMD	13	-0.041	(-0.182, 0.101)	0.574	0.146	0.003	0.852
Sleep duration	FN-BMD	56	0.001	(-0.001, 0.004)	0.337	0.266	0.007	0.109
	LS-BMD	55	-0.002	(-0.005,0.001)	0.243	0.172	0.009	0.095
Short sleep duration	FN-BMD	18	0.055	(-0.061, 0.171)	0.352	0.530	0.017	0.105
	LS-BMD	18	0.010	(-0.151, 0.171)	0.904	0.113	0.004	0.765
FN-BMD, the bone mineral density at the femoral neck; LS-BMD, the bone mineral density at the lumbar spine.								

MR analysis

In the MR analysis of the genetic variants, the results did not provide sufficient evidence to support a causal association between sleep disorders and BMD at either the femoral neck or lumbar spine. Using the IVW method, the estimated coefficients were negative for both femoral neck (β: -0.039; 95% CI: -0.142 to 0.063) and lumbar spine (β: -0.041; 95% CI: -0.182 to 0.101); however, the wide confidence intervals include 0, indicating no statistically significant associations. These findings do not support a causal relationship and are inconsistent with the observational data.The weighted median method(femoral neck: β -0.080, 95% CI -0.215 to 0.056; lumbar spine: β -0.054, 95% CI -0.229 to 0.121), MR Egger (femoral neck: β -0.052, 95% CI -0.454 to 0.350; lumbar spine: β -0.095, 95% CI -0.676 to 0.485) and Simple mode (femoral neck: β -0.070, 95% CI -0.327 to 0.187; lumbar spine: β -0.120, 95% CI -0.454 to 0.214) showed consistent effect estimates(Table S3)(Fig. 3). There was no evidence of pleiotropic effects in the MR analysis, with p-values of 0.950 and 0.852 for the femoral neck and lumbar spine, respectively. The potential heterogeneity was also not found(p = 0.641, 0.146 for the femoral neck and lumbar spine respectively). The funnel plot and leave-one-out plot of sleep disorder were displayed in Figure S1 and S2.

In MR analysis investigating the causal association between sleep duration and the BMD, no evidence was found for femoral neck (β: 0.001; 95% CI: -0.001 to 0.004) and lumbar spine (β: -0.002; 95% CI: -0.005 to 0.001) using IVW method. The effect estimate was confirmed by the weighted median method, MR Egger, Simple mode and Weighted mode (Fig. 4) (Table S3). Meanwhile, the MR Egger regression detected no pleiotropic effect (p = 0.109, 0.095 for the femoral neck and lumbar spine respectively). And no significant heterogeneity was found (p = 0.266, 0.172 for the femoral neck and lumbar spine respectively) among the selected SNPs. The funnel plot and leave-one-out plot of sleep duration were displayed in Figure S3 and S4.

In MR analysis investigating the causal association between short sleep duration and the BMD, the results of IVW showed no significant difference for femoral neck (β: 0.055; 95% CI: -0.061 to 0.171) and lumbar spine (β: 0.010; 95% CI: -0.151 to 0.171). The weighted median method, MR Egger, Simple mode and Weighted mode also indicated similar results (Fig. 5) (Table S3). There was no pleiotropic effect (p = 0.105, 0.765 for the femoral neck and lumbar spine respectively) or heterogeneity (p = 0.530, 0.113 for the femoral neck and lumbar spine respectively) in the included SNPs. The funnel plot and leave-one-out plot of short sleep duration were displayed in Figure S5 and S6.

Discussion

To the best of our knowledge, this study represents the first investigation into the association between sleep disorders, sleep duration, and BMD at the femoral neck and lumbar spine, measured by DXA, with combination of the NHANES database and MR analysis. Our observational study findings reveal a negative association between sleep disorders and BMD at both the femoral neck and lumbar spine;. On the other hand, no significant relationship was observed between sleep duration and BMD. Furthermore, stratified analysis by sleep disturbance did not support a conclusive relationship between sleep duration and BMD. Our MR analysis found no evidence of a causal relationship between sleep disorders or sleep

duration and BMD. This suggests that the associations observed in observational studies may be due to confounding factors rather than a true causal relationship, which could also explain the inconsistent findings reported in the literature.

Existing literature has yielded inconsistent findings regarding the association between sleep disorders and BMD. In a 10.7-year prospective cohort study of older adults, no significant association was observed between sleep disorders and BMD at the hip, spine, or total body. In contrast, Yen et al. reported that participants with either apnea-related or non-apnea-related sleep disorders had a higher incidence of osteoporosis compared to those without sleep disorders[30]. Furthermore, a prior meta-analysis of cross-sectional studies indicated that individuals with sleep problems were at greater risk of developing osteoporosis[31]. In our present study, we observed a negative relationship between sleep disorders and BMD in a large-scale cohort after adjusting for known confounders. However, the MR analysis did not yield statistically significant results with genetic variants related to sleep disorders and BMD. As is mentioned above, MR studies are less susceptible to be confounded by other factors compared to the observational studies. This discrepancy could be attributed to several factors. Firstly, the sample size in the MR analysis might not have been sufficiently large to detect a significant association. Secondly, the genetic variants used as instruments in the MR analysis may not have been strong enough predictors of sleep disorders, leading to weak instrument bias. Additionally, there could be other unmeasured genetic or environmental factors that influence both sleep disorders and BMD, which were not accounted for in the MR analysis.To date, limited research has explored the mechanisms underlying bone loss associated with sleep disorders. Increased sympathetic nervous activity caused by sleep deprivation and fragmentation has been identified as a key contributor[32]. Elevated sympathetic activity may enhance bone resorption and suppress bone formation through leptin-induced signaling[33]. Moreover, obstructive sleep apnea has been implicated in exacerbating bone loss through multiple pathways[34], including oxidative stress[35], elevated inflammatory markers[36], and altered glucocorticoid regulation[34]. Consistent with previous studies[10,14,37], our findings support a significant association between sleep disorders and DXA-measured BMD in observation study. However, variations in the criteria used to define short or long sleep duration, participants' baseline conditions, and methods of measuring BMD across studies may contribute to the observed heterogeneity in results. Therefore, further randomized controlled trials (RCTs) are needed to clarify these associations.

In our study, BMD at the femoral neck and lumbar spine was measured using DXA in both the observational and MR studies, providing strong evidence for clinical applications. DXA is widely regarded as the gold standard for assessing osteoporosis risk, offering key advantages such as the highest accuracy in predicting hip fracture risk, the ability to integrate BMD results into the World Health Organization's osteoporosis definition using T-scores, and the utility for monitoring therapeutic responses[38]. In contrast, previous studies[32,39] have often relied on quantitative ultrasound (QUS) systems to measure BMD or bone stiffness. While QUS has been shown to have comparable accuracy to DXA in measuring BMD[32], it is less effective for diagnosing bone loss in patients with certain specific diseases, limiting the generalizability of those findings[40–42].

This study has several strengths. First, it is based on a large, nationally representative sample of the U.S. population, which enhances the generalizability of the findings. Second, BMD was measured at the femoral neck and lumbar spine using DXA, which is considered the current gold standard for diagnosing osteoporosis, providing comprehensive reference data for clinical applications. Addition, to the best of our knowledge, this is the first study to describe the association between BMD, sleep disturbance and sleep duration conducted with NHANSE study, one of the large population based databases, thus providing another evidence for their correlation.However, our study also has limitations. First, information on sleep duration in the NHANES database was self-reported, which introduces the potential for information bias. Participants may underreport or overreport their sleep time, leading to misclassification. Second, due to the limited number of SNPs associated with long sleep duration in the primary GWAS study[26], we were unable to include long sleep duration in the MR analysis, limiting the comprehensiveness of our results. Additionally, MR analysis reflects long-term exposure to sleep problems, and it remains unclear whether short-term changes in sleep habits influence bone metabolism. This warrants further investigation in RCTs.

Conclusion

The findings of this large-scale cohort and MR analysis do not provide evidence for a causal association between sleep disorders or sleep duration and higher risk of bone loss. The observational analyses suggested weak associations, but these were not supported by the MR results, which are less susceptible to confounding. Additionally, no evidence was found to suggest that extending sleep duration could mitigate bone loss associated with sleep disorders. These results underscore the importance of further validation through randomized controlled trials and a more detailed exploration of the mechanisms and subtypes of sleep disorders in future studies.

Declarations

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Author contributions

RC, JX and ZL conceived the idea, designed the methodology and drafted the manuscript. JC, HX and ZZ searched the original data. FC and KC conducted statistical analysis. JX revised the manuscript. All authors contributed to the article and approved the submitted version.

Data availability statement

The data supporting the findings of this study are accessible via NHANES (National Health and Nutrition Examination Survey) at https://wwwn.cdc.gov/nchs/nhanes/. Additionally, the Mendelian study data were obtained from the UK Biobank (http://www.nealelab.is/uk-biobank) for sleep duration, the FinnGen database (https://www.finngen.fi/en/access_results) for sleep disorders, and the GEFOS Consortium (http://www.gefos.org/) for bone mineral density.

Ethical approval

The Research Ethics Review Board of NCHS (National Centre for Health Statistics) reviewed and approved NHANES, and written informed consent had been acquired from all participants in this study. The original GWASs received ethical approval from the relevant ethics review committees; therefore, no additional ethical approval was required.

Competing interests

Zhiqin Liu, Jian Xu,Zilong Yang,Zihao Deng and Renqiang Chen declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

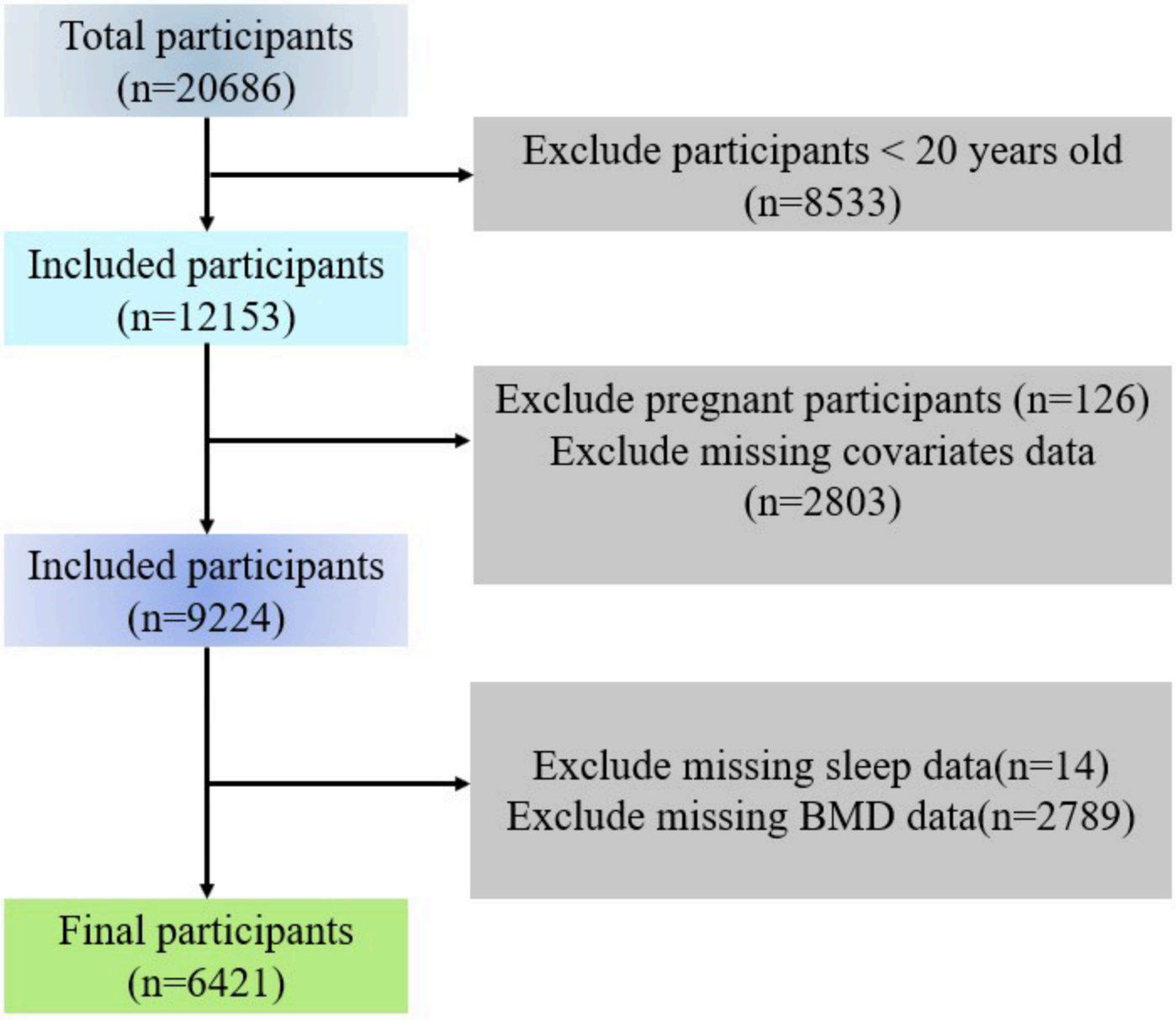

Figure 1

Flowchart of the participant inclusion.

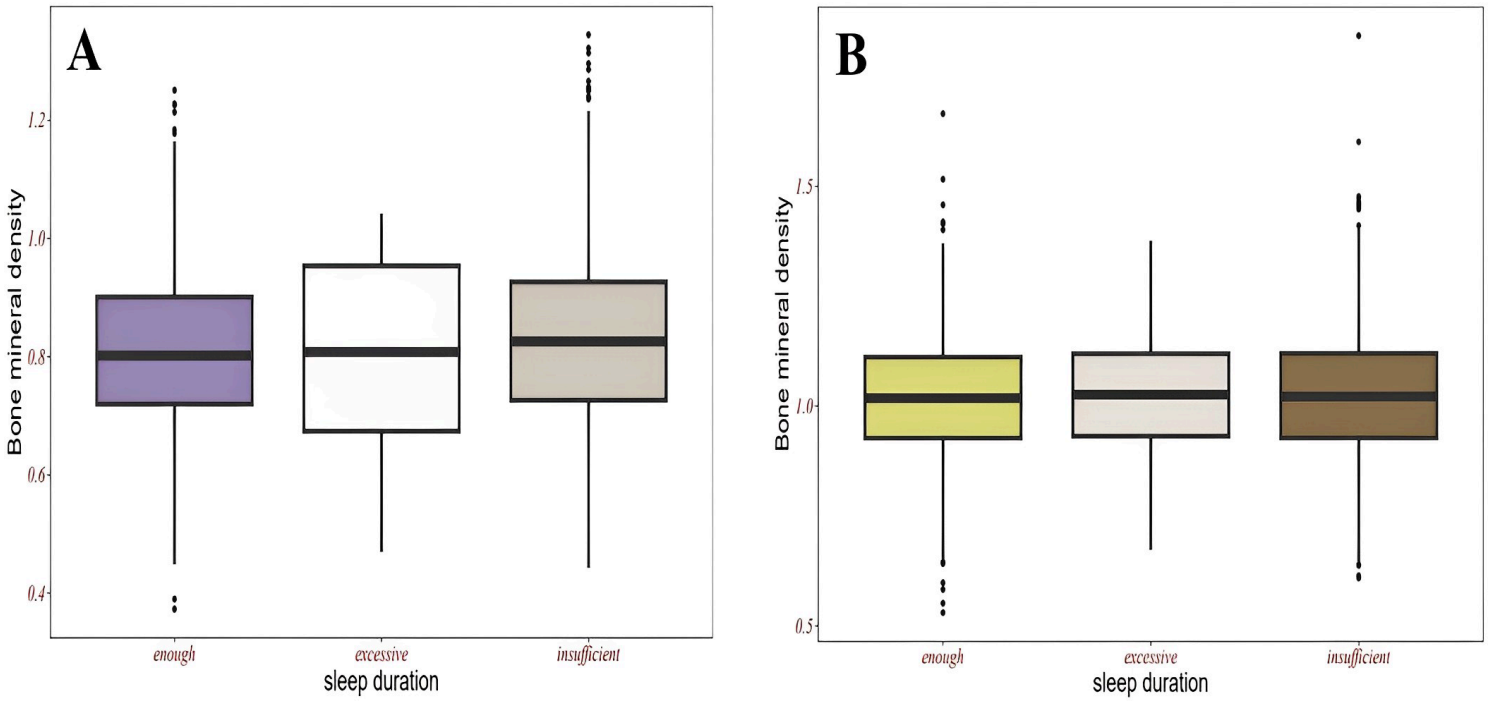

Figure 2

The BMD distribution of in participants with sleep disturbance by sleep duration. A) femoral neck B) lumbar spine.

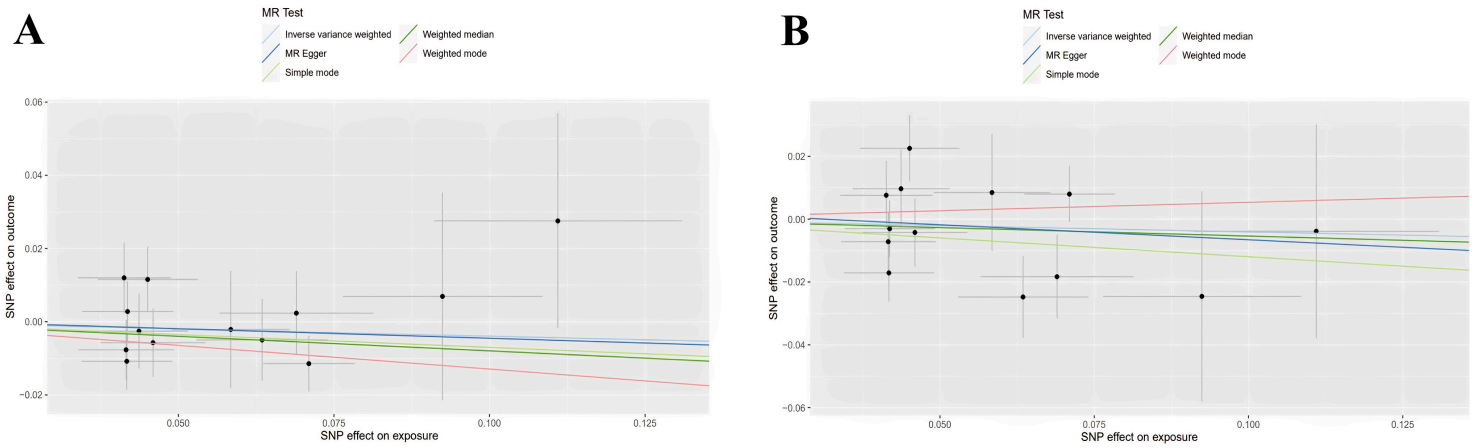

Figure 3

Scatter plots for MR analyses of the causal effect of sleep disorder on BMDs. A) femoral neck; B) lumbar spine.

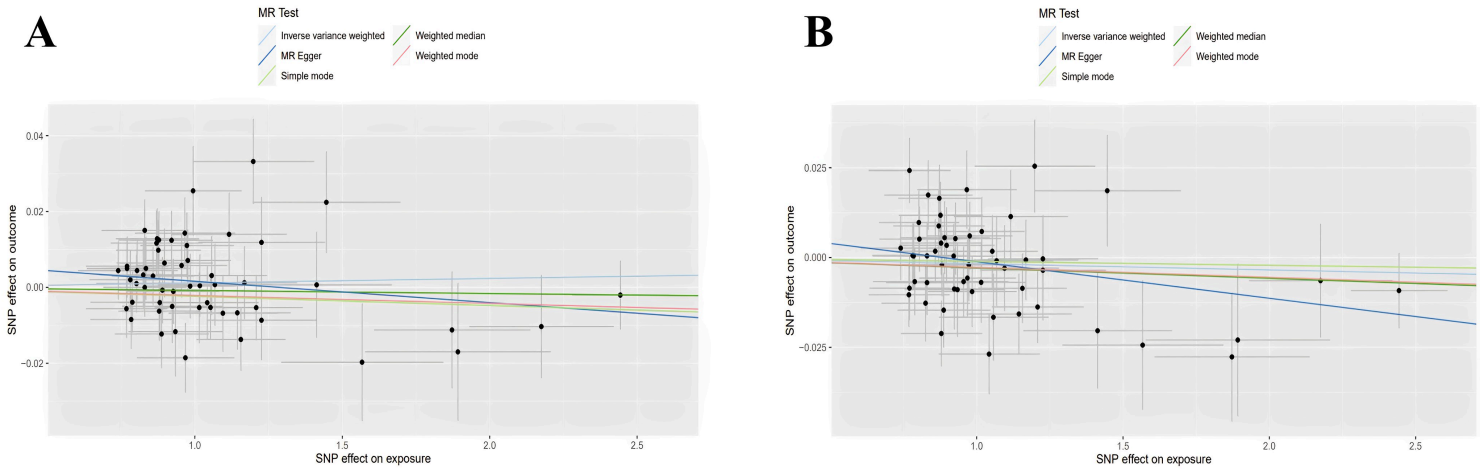

Figure 4

Scatter plots for MR analyses of the causal effect of sleep duration on BMDs. A) femoral neck; B) lumbar spine.

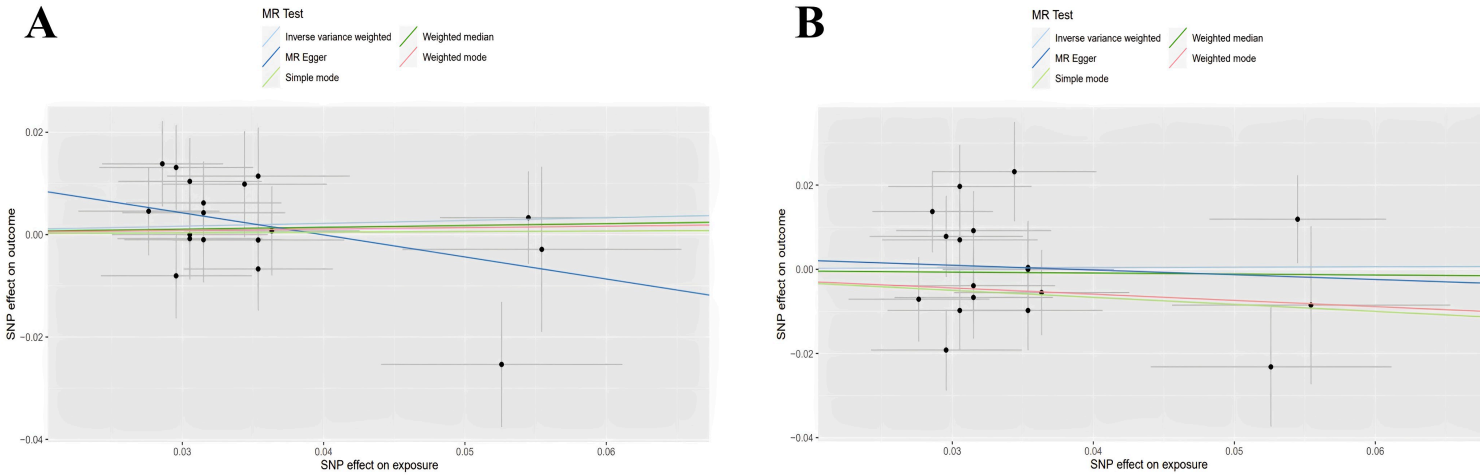

Figure 5

Scatter plots for MR analyses of the causal effect of short sleep duration on BMDs. A) femoral neck; B) lumbar spine.

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