A causal relationship between sleep behaviour and osteoporosis: a two-sample reverse-mediated Mendelian randomisation study

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Research Article

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Abstract

Background
In recent years, there have been more and more clinical observational studies on sleep behaviour and osteoporosis, but the causal relationship between sleep behaviour and osteoporosis at the genetic level, and whether there are mediating factors between the two is still unclear.

Methods
From the published GWAS data, seven sleep behaviours were selected as exposure factors: insomnia, sleep time, getting up in the morning, napping during the day, sleep type (early/late rise), narcolepsy and snoring. Bone mineral density of heel (H-BMD), forearm (FA-BMD), lumbar vertebra (LS-BMD) and femoral neck (FN-BMD) were the outcome factors. The causal relationship between low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) was analyzed through Mendelian randomization.

Results
The results of a two-sample Mendelian randomization study showed that snoring was positively correlated with lumbar bone density (OR = 1.555, 95%CI: 1.189–2.032, P = 0.001). The results of reverse Mendelian randomization showed that lumbar bone density was not the cause of snoring (P = 0.466). Mediating Mendelian randomization studies showed that both LDL cholesterol and triglycerides had mediating effects on sleep behaviour and bone density (OR = 0.92, 95%CI: 0.87–0.98, P = 5.56e-3) (OR = 1.17, 95%CI: 1.09–1.26, P = 3.72e-5).

Conclusions
Our study shows that snoring is a factor affecting lumbar bone density, and low-density lipoprotein cholesterol and triglyceride play an intermediary role in it. Therefore, correcting snoring and controlling low-density lipoprotein cholesterol and triglyceride index should be included in the clinical regimen for preventing and treating bone mineral density decline.

1. Background
With the development of modern society, the improvement of economic level, and the advancement of medical technology, the life expectancy of human beings has been greatly extended, which has aggravated the ageing of the social population, and the incidence of diseases related to ageing has also greatly increased [1]. Osteoporosis has become a common systemic metabolic bone disease, which is characterised by a decrease in bone mass, degradation of the microstructure of bone as the main pathological features and susceptibility to fracture as the main clinical manifestations [2]. Its onset is closely related to ageing, female gender, and a wide range of clinical, medical, behavioural, nutritional and genetic factors [3–7]. Nowadays,
dual-energy X-ray (DXA) measurement of bone mineral density in the lumbar spine, proximal femur, and distal forearm is mainly used clinically as the gold standard for the diagnosis of osteoporosis [8]. The United Nations predicts that by 2100, the global ratio of people over 65 years of age to those aged 15–64 years will triple, and as a result, the prevalence of osteoporosis will also climb rapidly [9–10]. With more than 8.9 million osteoporotic fractures occurring globally every year, one osteoporotic fracture every three seconds, and roughly €31 billion and $13.7–20.3 billion spent on treating osteoporotic fractures in the European Union and the United States of America, respectively, in 2010, osteoporosis is a significant and costly health problem [11–12]. A large number of existing studies have shown that unhealthy lifestyle, glucocorticoid therapy, low body mass index (BMI), physical inactivity, gastrointestinal disorders, haematological disorders, and calcium and vitamin D deficiencies may be risk factors for low BMD and fracture occurrence [5, 13–14].

A cross-sectional study published by Yuchen Tang showed that unhealthy sleep duration, especially prolonged sleep, was associated with decreased bone mineral density; a clinical observational study published by Yang Yanqiong and others showed that, in the population of postmenopausal females, excessive sleep duration and late sleep onset were risk factors for increased risk of osteoporosis, and that the later the sleep onset, the higher the risk of osteoporosis The later the sleep time, the higher the risk of osteoporosis. A cross-sectional study of sleep duration and bone mineral density in Japan showed that too little sleep was an important factor in the decline of bone mineral density [15–17]. However, all these clinical studies are susceptible to confounding factors and reverse causality.

Genetic epidemiology has emerged as an important method of revealing disease factors, assigned before birth and fixed at conception [18], not confounded by other risk factors, in this way reducing the influence of confounding factors and avoiding reverse causation bias, thus yielding causal effects that are more reliable than observational studies [19–21]. Mendelian randomisation uses exposure-related genetic variation as an instrumental variable to robustly assess the causal relationship between exposure and outcome, which has emerged as an alternative approach to studying causality [22–23]. As shown in Fig. 1, the flow chart of the two-sample reverse mediated Mendelian randomization research method is shown.

A review of published Mendelian randomised studies reveals a negative causal association between sleep duration in sleep behaviour and the risk of developing osteoarthritis of the knee; osteoporosis may be associated with an increased risk of osteoarthritis; and there is a causal association between elevated levels of LDL cholesterol and reduced heel bone density [24–26]. In addition, a study based on the NHANES database showed a significant positive correlation between the triglyceride glucose index steady-state model assessment and its associated indices and BMD [27]; therefore, this paper uses two-sample bidirectional multivariate mediated Mendelian randomisation to elucidate whether there is a causal relationship between different sleep behaviours and BMD at different sites as well as to discuss whether there is a positive correlation between LDL and triglyceride potential mediating role between sleep behaviour and BMD.

This is the first Mendelian randomisation article to explore the causal relationship between sleep behaviour and osteoporosis.

2. Methods
2.1. All data sources

Exposure and outcome factors were analyzed using 7 sleep behaviors and 4 site bone mineral density data from the big data of the genome-wide association study (GWAS). All the data from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). Table 1 shows the consortium of all GWAS data, GWAS ID, population, number of SNPS, sample size, year, and gender. In addition, all participants were of European descent, which reduces population bias to some extent.
Table 1
the consortium of all GWAS data, GWAS ID, Population, Number of SNPS, Sample size, Year, and Sex

<table>
<thead>
<tr>
<th>Exposure or outcome</th>
<th>Consortium</th>
<th>GWAS ID</th>
<th>Population</th>
<th>Number of SNPs</th>
<th>Sample size</th>
<th>Year</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>MRC-IEU</td>
<td>ukb-b-3957</td>
<td>European</td>
<td>9851867</td>
<td>462341</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>MRC-IEU</td>
<td>ukb-b-4424</td>
<td>European</td>
<td>9851867</td>
<td>460099</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Getting up in the morning</td>
<td>MRC-IEU</td>
<td>ukb-b-2772</td>
<td>European</td>
<td>9851867</td>
<td>461658</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Nap during day</td>
<td>MRC-IEU</td>
<td>ukb-b-4616</td>
<td>European</td>
<td>9851867</td>
<td>462400</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Chronotype</td>
<td>MRC-IEU</td>
<td>ukb-b-4956</td>
<td>European</td>
<td>9851867</td>
<td>413343</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>MRC-IEU</td>
<td>ukb-b-5776</td>
<td>European</td>
<td>9851867</td>
<td>460913</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Snoring</td>
<td>MRC-IEU</td>
<td>ukb-b-17400</td>
<td>European</td>
<td>9851867</td>
<td>430438</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Heel Bone mineral density</td>
<td>MRC-IEU</td>
<td>ukb-b-20124</td>
<td>European</td>
<td>9851867</td>
<td>265753</td>
<td>2018</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Femoral neck bone mineral density</td>
<td>GEFOS</td>
<td>ieu-a-980</td>
<td>Mixed</td>
<td>10586900</td>
<td>32735</td>
<td>2015</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Forearm bone mineral density</td>
<td>GEFOS</td>
<td>ieu-a-977</td>
<td>Mixed</td>
<td>9955366</td>
<td>8143</td>
<td>2015</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Lumbar spine bone mineral density</td>
<td>GEFOS</td>
<td>ieu-a-982</td>
<td>Mixed</td>
<td>10582867</td>
<td>28498</td>
<td>2015</td>
<td>Males and Females</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol levels</td>
<td>NA</td>
<td>ebi-a-GCST90002412</td>
<td>European</td>
<td>16293344</td>
<td>431167</td>
<td>2020</td>
<td>NA</td>
</tr>
</tbody>
</table>
### 2.2. Screening for instrumental variables

To obtain stable estimates, the screening of instrumental variables for Mendelian randomisation analyses requires strict adherence to the following three assumptions: i) the assumption of association: the selected independent instrumental variable is directly related to the exposure factor; ii) the assumption of independence: the selected instrumental variable is not related to any confounding variables between the exposure and the outcome; and iii) the assumption of exclusion: the selected instrumental variable does not affect the outcome, except through its association with the exposure [24]. SNPs were considered instrumental variables when they fulfilled the above three assumptions.

As an extension of two-sample Mendelian randomization, reverse Mendelian randomization uses the same method as above to calculate the causality between outcome factors and exposure factors. Intermediate Mendelian randomization incorporates all exposures into the same model to calculate their effect on outcomes.

This study used SNPs at the genome-wide significance threshold and linkage disequilibrium (r^2 < 0.001, 10,000kb) as potential tools to ensure that screening for instrumental variables was the assumption of association that needed to be ensured [28]. The PhenoScanner (http://www.phenoscan.medschl.cam.ac.uk/) database was searched within the study to ascertain that the selected SNPs were not associated with potential confounders to ensure independence and exclusivity of the instrumental variables [24].

### 2.3. Mendelian randomisation analysis

Using our data described above, a two-sample Mendelian randomisation analysis was used to explore the relationship between sleep behaviour and BMD at each site. The instrumental variables were aligned to the effect alleles of the ending SNPs, and all SNPs with palindromic structures were deleted. To reduce the bias of the weak instrumental variables, the F-statistic of each SNP was calculated individually, and then the weak instrumental variables with F-statistic < 10 were filtered, and then the presence of outliers was determined by the MR-PRESSO test and they were deleted [29].

Often the inverse variance weighting (IVW) algorithm is considered the primary method for determining exposure versus outcome, and to ensure the robustness of the results we also used Mendelian randomised regression (MR-Egger), the weighted median method (WME), the weighted model (WM), and a simple weighted model (SM) to estimate the exposure on outcome effects [30–34].

### 2.4. Sensitivity analyses

We used Cochran's Q test to test for heterogeneity, and with a p-value of 0.05 indicating greater heterogeneity, a random-effects model was chosen; MR-Egger regression was used to assess the potential pleiotropy of
SNPs as IVs. The intercept term in MR-Egger regression can be a useful indicator of the presence of directional level pleiotropy; the use of the leave-one-out method to determine the presence of outlier effects. A threshold of \( P < 0.05 \) was used for all sensitivity analyses [31].

2.5. Ethics.

Our analyses used published studies or publicly available GWAS pooled data. No primary data were collected in this paper and therefore ethics committee approval was not required. Each study included was approved by its institutional ethics review board and all participants provided written informed consent.

All data were analysed using the TwoSampleMR package in version R4.3.1 [35].

3. Results

3.1. Two-sample Mendelian randomisation

The results of two-sample Mendelian randomisation showed that snoring was positively and causally associated with lumbar spine bone density, and snoring was a risk factor for lumbar spine bone density.

From the snoring-associated GWAS data, the data were extracted under the threshold of genome-wide significance (when screening for snoring-associated SNPs, the significance threshold of the data was relaxed to \( p < 5e-6 \), and usually \( p < 5e-8 \) is required for genome-wide significance; however, the number of SNPs screened under the threshold was small, and therefore the threshold was appropriately adjusted downward, which may have some impact on the findings) and the removal of the chain imbalance \( (r2 = 0.001 \) and \( kb = 10000) \) as instrumental variables; five SNPs associated with confounders were removed (rs8041579 rs2968274 rs11205823 rs57222984 rs78975623); and the instrumental variables were matched with lumbar spine bone mineral density data, and all SNPs with palindromic structures were removed (rs10475978 rs11041980 rs1558901 rs227727 rs7740797 rs9642200); the MR-PRESSO test had no outliers \( (p = 0.583) \) and the F-statistics of the SNPs were all greater than 10, with no weak instrumental variables.

Heterogeneity of instrumental variables was detected using Cochran's Q test, and the IVW results showed \( p > 0.05 \) (as shown in Table 2), so there was no heterogeneity between instrumental variables, and therefore causality was explored using the fixed-effects model. The results are shown in Table 3.

According to the IVW results in MR analysis, we found a positive causal relationship between snoring and lumbar spine bone density \( (b = 0.441, \text{OR} = 1.555, p = 0.001) \), and almost all of the five methods of Mendelian randomisation analysis had an OR value > 1, which suggests that snoring may be a risk factor for lumbar spine bone density.
Table 2
Cochran's Q test results

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Cochran's Q</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MR Egger</td>
</tr>
<tr>
<td>Snoring</td>
<td>Lumbar spine bone mineral density</td>
<td>0.574</td>
</tr>
</tbody>
</table>

Table 3
Results of MR study analysing snoring and lumbar spine bone density

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Methods</th>
<th>Lumbar spine bone mineral density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>nSNP</td>
</tr>
<tr>
<td>Snoring</td>
<td>MR Egger</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>WME</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>IVW(p = 5e-6)</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>SM</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>144</td>
</tr>
</tbody>
</table>

The calculation of the test of polytropy is shown in Table 4 below, p = 0.929 (p > 0.05), the calculation is not significant, so there is no polytropy and the results are relatively stable.

Table 4
Multiple validity test

<table>
<thead>
<tr>
<th>id:ukb-b-17400</th>
<th>exposure</th>
<th>egger_intercept</th>
<th>se</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-0.000</td>
<td>0.004</td>
<td>0.929</td>
</tr>
</tbody>
</table>

The calculation results of the rejection-by-exclusion test are shown in Fig. 2 below, all results are on the right side of zero, so the results are relatively stable and there is a positive causal association between the two.

All results are now visualised (as shown in Figs. 3–5) and the results are as follows. The scatter plot (as shown in Fig. 3) showed that snoring and lumbar spine bone density were positively causally related in the IVW results; the forest plot (as shown in Fig. 4) showed that ALL ME-Egger was across zero, which was not significant, so there was no horizontal polytropy, which was the same as the conclusion of the results mentioned above [31]; ALL IVW was on the right side of zero, that is, snoring and lumbar spine bone density had a positive causality, so the more severe snoring during sleep, the more severe the damage to lumbar spine bone density, the greater the degree of damage to lumbar spine bone density. The funnel plot (Fig. 5) showed that the SNPs were probably symmetrically distributed, so the results were relatively stable.

3.2. Inverse Mendelian randomization

In the study exploring the causal relationship between lumbar spine bone density and snoring, all SNPs with significant correlation levels (p < 5e-8) and chained imbalance ((r2 < 0.001, 10,000kb) were extracted from the
lumbar spine bone density GWAS data and analysed concerning snoring in a Mendelian randomisation analysis, the results of which are shown in Table 5 below.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Methods</th>
<th>nSNP</th>
<th>b</th>
<th>SE</th>
<th>pval</th>
<th>OR</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine bone mineral density</td>
<td>MR Egger</td>
<td>22</td>
<td>0.020</td>
<td>0.016</td>
<td>0.236</td>
<td>1.020</td>
<td>0.988</td>
<td>1.054</td>
</tr>
<tr>
<td></td>
<td>WME</td>
<td>22</td>
<td>0.002</td>
<td>0.005</td>
<td>0.735</td>
<td>1.002</td>
<td>0.992</td>
<td>1.011</td>
</tr>
<tr>
<td></td>
<td>IVW(p = 5e-8)</td>
<td>22</td>
<td>0.003</td>
<td>0.004</td>
<td>0.466</td>
<td>1.003</td>
<td>0.996</td>
<td>1.010</td>
</tr>
<tr>
<td></td>
<td>SM</td>
<td>22</td>
<td>0.002</td>
<td>0.008</td>
<td>0.818</td>
<td>1.002</td>
<td>0.985</td>
<td>1.019</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>22</td>
<td>0.004</td>
<td>0.008</td>
<td>0.580</td>
<td>1.004</td>
<td>0.990</td>
<td>1.019</td>
</tr>
</tbody>
</table>

As shown in Table 5 above, the IVW algorithm p = 0.466 (p > 0.05), so lumbar spine bone density was not an influencing factor for snoring.

### 3.3. Mediated Mendelian randomisation

Multivariate Mendelian randomization analysis was used to investigate the mediating effect of low-density lipoprotein cholesterol and triglyceride on snoring and lumbar bone density. The results showed that both low-density lipoprotein and triglyceride played a significant intermediary role, as shown in Table 6 below.

<table>
<thead>
<tr>
<th>Mediated Mendelian randomization</th>
<th>Exposure</th>
<th>SNP</th>
<th>b</th>
<th>SE</th>
<th>OR</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring and lumbar bone density</td>
<td>LDL</td>
<td>240</td>
<td>-0.08</td>
<td>0.03</td>
<td>0.92</td>
<td>0.87</td>
<td>0.98</td>
<td>5.56e-3</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>154</td>
<td>0.16</td>
<td>0.04</td>
<td>1.17</td>
<td>1.09</td>
<td>1.26</td>
<td>3.72e-5</td>
</tr>
<tr>
<td></td>
<td>Snoring</td>
<td>15</td>
<td>0.41</td>
<td>0.29</td>
<td>1.50</td>
<td>0.84</td>
<td>2.68</td>
<td>1.67e-1</td>
</tr>
</tbody>
</table>

It can be calculated that the mediating effect of LDL and triglyceride is 0.034, and the ratio of the mediating effect between the two is 0.077.

### 4. Discussion

Osteoporosis is one of the main causes of fractures in the elderly, and since effective prevention and treatment options are limited, it is essential to reduce the incidence of the disease through lifestyle changes.
Although some previous studies have also shown a link between sleep behaviour and bone density. For example, a clinical study using a multivariate logistic regression model showed that poor sleep behaviour was significantly associated with an increased risk of low bone mineral density, and most patients with senile osteoporotic fractures also had unhealthy sleep behaviour [36]. Sleep characteristics, including sleep apnea, daytime and nighttime sleep duration, and daytime naps, have also been associated with the onset of osteoporosis [37]. In particular, it should be noted that obstructive sleep apnea-hypopnea syndrome (OSAHS) can also affect bone metabolism through the hypoxia caused by OSAHS, which is mainly manifested by the decrease of volumetric bone density, tibial cortex and bone trabecular thickness, thus increasing the risk of osteoporosis [38–40]. At the same time, a multi-centre study showed that patients with OSAHS were more likely to develop sarcopenia and osteoporosis; A prospective cohort study of snoring in Korean women showed that the frequency of snoring may be related to the incidence of fragility fractures, and observing the frequency of snoring can improve the accuracy of brittle-fracture risk prediction [41–42]. However, to further explore the relationship between sleep behaviour and bone mineral density, we conducted a two-sample Mendelian randomization analysis using the IEU Open GWAS public database. The results showed that there was a positive causal relationship between snoring and lumbar bone density during sleep, that is, the severity of snoring during sleep was positively correlated with the decrease of lumbar bone density.

In addition, based on the results of the two-sample Mendelian randomization study, we conducted a preliminary exploration of the potential mechanism of snoring that may affect lumbar bone density. Using a multivariate approach to intermediate Mendelian randomization, we determined a causal relationship between triglyceride and low-density lipoprotein cholesterol-mediated snoring and lumbar bone density. While the study provides valuable insights into the relationship between sleep behaviour and bone density, further research is needed to understand the underlying mechanisms in more detail.

Previous Mendelian randomized studies have shown that osteoarthritis is causally related to bone mineral density, sleep disorders, and lower LDL cholesterol levels [43]. A study using the NHANES database showed that LDL cholesterol is negatively correlated with lumbar bone density, and measuring LDL cholesterol can be used as a reactive biomarker for early detection of osteoporosis and guidance for treatment [44]. As for the relationship between triglycerides and bone mineral density, it was mentioned in a cross-sectional study on type 2 diabetes in African Americans, which suggested that there was a contradictory relationship between vitamin D and BMD status and TG levels in African Americans [45]. All these kinds of literature provided a theoretical basis for us to explore the potential mediating role of LDL cholesterol and triglycerides in the relationship between sleep behaviour and bone mineral density and confirmed the mediating role of both by mediating Mendelian randomization. However, the mediating rate was 7.7%, so the clinical significance of this mediating factor may be limited.

This study has several important advantages, first, it is the first two-sample bidirectional mediated MR Study to investigate the causal relationship between sleep behaviour and bone mineral density, which is the closest approach to RCT and allows for random assignment based on genotype. This study design can avoid some limitations of traditional observational studies, including reverse causality and potential confounding factors, and significantly expand relevant research [46]. Second, we have taken several steps to meet MR's core assumptions. Specifically, instrumental variables for sleep behaviour were derived from large-scale GWAS
data, which provided strong and reliable genome-wide association SNPS and avoided potentially weak instrumental biases. This gives it sufficient statistical validity to estimate causality. These advantages all enhance the credibility of the research results [47].

From the perspective of traditional clinical research, poor sleep behaviour has been proven to be a risk factor for bone mineral density loss. In this study, we selected SNPS with genome-wide associations and independent genetics with the removal of linkage imbalances as instrumental variables to assess the causal relationship between sleep characteristics and bone mineral density, which makes our results more robust. In addition, both the pleomorphy test and the one-by-one elimination test were negative, indicating that our results are robust.

Nevertheless, some limitations of MR Analysis need to be considered. First, the aggregated GWAS data are mostly for individuals of European descent, so it is debatable whether our results are fully representative of the entire population. Therefore, we should be cautious about applying our conclusions to populations of different races and ethnicities. Secondly, we cannot rule out the influence of confounding factors on the results. Even if we use such methods as MR Egger and MR-PROSSO to control confounding factors, it is necessary to recognize that residual confounding factors may still exist. Finally, our study focused only on the mediating role of triglycerides and LDL cholesterol, ignoring other potential factors that have not yet been explored.

5. Conclusion

In summary, in this study, we aimed to evaluate the causal relationship between sleep behaviour (including insomnia, sleep duration, morning wake up, daytime napping, early/late rise, narcolepsy, and snoring) and BMD at four sites (heel BMD, forearm BMD, femoral neck BMD, and lumbar BMD) by using two-sample two-way mediated MR Analysis. We found that snoring is positively correlated with lumbar bone density and may be a risk factor; that is, snoring during sleep is not conducive to the improvement and stability of lumbar bone density; Reverse MR Analysis showed that lumbar bone density was not a factor affecting snoring. Intermediate MR Analysis showed that LDL cholesterol and triglycerides play a potential mediating role in the causal relationship between snoring and lumbar bone density. More importantly, this study explains the causal relationship between sleep behaviour and the increase or decrease of bone mineral density from the perspective of genetics, which also reminds clinicians to consider sleep behaviour when treating patients with osteoporosis, and provides a new idea for clinical prevention and treatment of osteoporosis. Of course, our conclusions need to be confirmed by further clinical and basic experiments.

Abbreviations

MR: Mendelian randomization; BMD: Bone density; H-BMD: heel bone density; FA-BMD: forearm bone density; FN-BMD: Bone density of femoral neck; TB-BMD: total body bone density; LS-BMD: Lumbar bone density; DXA: Dual-energy X-ray absorptiometer; GEFOS: Genetic Factors of Osteoporosis Association website; GWAS: Genome-wide association study; IVs: tool variable; LD: linkage imbalance; SNP: single nucleotide polymorphism; RCT: randomized controlled trial; IVW: inverse variance weighting; WMM: weighted median;
MR-Egge: Mendelian randomized regression; WM: weighted mode; SM: Simple weighting model; NHANES: National and Nutrition Examination Survey

Declarations

6.2. Acknowledgements

Not applicable

6.3. Authors’ contributions

Y.W. came up with the idea for the study.

Y.W. gets genetic data.

Y.W. performs data analysis.

Y.W. explained the results of the data analysis.

All the authors have written manuscripts.

All authors read and approved the final manuscript.

6.4. Funding

Not applicable

6.5. Availability of data and materials

The datasets supporting the conclusions of this paper are available in the IEU Open GWAS repository.

IEU Open GWAS provides GWAS summary statistics for sleep behavior and bone mineral density.

Additional data generated or analysed in the course of this study are available in this published article and its supplementary information document.

6.6. Ethics approval and consent to participate

Not applicable

6.7. Consent for publication

Not applicable

6.8. Competing interests

The authors declare that they have no competing interests.

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38. OPG/RANKL - .
40. - .

Figures
Figure 1

Flow chart of two-sample reverse-mediated Mendelian randomization
Figure 2

Preliminary calculation of snoring and lumbar spine bone density causality MR study by elimination test
Figure 3

Scatter plot of MR study on the causal relationship between snoring and lumbar spine bone density in the preliminary calculation.
Figure 4

Forest plot of the MR study of the causal relationship between snoring and lumbar spine bone density in the preliminary calculations
Figure 5

Funnel plot of the MR study of the causal relationship between snoring and lumbar spine bone density in the preliminary calculations