Assessment of causal association between the socio-economic status and osteoporosis and fractures: A bidirectional Mendelian randomization study in European population

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Acknowledgements & Funding

This work was supported by the National Natural Science Foundation of China (No.82370892, 82070910, 82100944 and 8210094), National Key Research & Development Program (No.2021YFC2501701), the Health Research Project in Hunan Province (No.20231696), the Natural Science Foundation of Hunan Province (No.2022JJ40721) and the Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University (No.7673). The authors acknowledge the consortia for their efforts in providing researchers with high-quality GWAS resources. This article does not contain any studies with human or animal subjects. Figures were created with biorender.com.
Abstract

Background

The relationship between socio-economic status and bone-related diseases is attracting increasing attention. Therefore, a bidirectional Mendelian randomization (MR) analysis was performed in this study.

Methods

Genetic data on factors associated with socio-economic status (average total household income before tax, years of schooling completed and Townsend Deprivation Index at recruitment), femoral neck bone mineral density (FN-BMD), heel bone mineral density (eBMD), osteoporosis, and five different sites of fracture (spine, femur, lower leg-ankle, foot, and wrist-hand fractures) were derived from genome-wide association summary statistics of European ancestry. The inverse variance weighted method was employed to obtain the causal estimates, complemented by alternative MR techniques, including MR-Egger, weighted median, and MR-pleiotropy residual sum and outlier (MR-PRESSO). Furthermore, sensitivity analyses, and multivariable MR was performed to enhance the robustness of our findings.

Results

A higher educational attainment was associated with an increased level of eBMD (beta:0.06, 95% CI:0.01-0.10, P=7.24×10^{-3}), and decreased risk of osteoporosis (OR:0.78, 95% CI:0.65-0.94, P=8.49×10^{-3}), spine fracture (OR:0.76, 95% CI:0.66-0.88, P=2.94×10^{-4}), femur fracture (OR:0.78, 95% CI:0.67-0.91, P=1.33×10^{-3}), lower leg-ankle fracture (OR:0.79, 95% CI:0.70-0.88, P=2.05×10^{-5}), foot fracture (OR:0.78, 95% CI:0.66-0.93, P=5.92×10^{-3}) and wrist-hand fracture (OR:0.83, 95% CI:0.73-0.95, P=7.15×10^{-3}). Further, material deprivation seemed to
harm the spine fracture (OR:2.63, 95% CI:1.43-4.85, P=1.91×10⁻³). A higher level of FN-BMD positively affected increased household income (beta:0.03, 95% CI:0.01-0.04, P=6.78×10⁻³). All these estimates were adjusted for body mass index (BMI), type 2 diabetes, smoking initiation, and frequency of alcohol intake.

Conclusions

The Mendelian randomization analyses show that higher educational levels is associated with higher eBMD, reduced risk of osteoporosis and fractures, while material deprivation is positively related to spine fracture. Enhanced FN-BMD correlates with increased household income. These findings offer valuable insights into the formulation of health guidelines and policy development.

Keywords: Osteoporosis, Fracture, Income, Education, Material deprivation, Mendelian randomization

Lay summary

We conducted stratified analyses to explore the causal links between socio-economic status and osteoporosis and various fractures and observed that education significantly reduced risk of osteoporosis and lower eBMD. It also lowered the risks of fractures of spine, femur, lower leg-ankle, foot, and wrist-hand, while material deprivation exhibited positive associations with spine fracture risk. Bidirectional MR analysis showed that an elevated score of FN-BMD was associated with a higher income level. Our study shows the importance of conducting routine BMD estimations and osteoporosis screening, to enhance knowledge and awareness among individuals to promote bone health and prevent fractures.
Introduction

Osteoporosis is defined as systemic decreased alteration of bone mass and strength with impaired microarchitecture, and is thought to be one of the most frequently encountered age-related disease today, increasing economic strains on individuals as well as the society and the government. The diagnosis of osteoporosis involves assessing bone mineral density (BMD) employing dual X-ray absorptiometry (DXA). Osteoporosis is defined by a T score falling 2.5 standard deviations or more below the average BMD of healthy young adults\(^1\). The most serious complication of osteoporosis is fragility fractures (FF), which most commonly occur in the spine, neck of the femur, or wrist. These fractures constitute the primary cause of mortality among older adults\(^2\). Currently, several hundred million adults either have osteoporosis or are at high risk of the condition, resulting in millions of FFs annually. By 2050, it is estimated that over 50% of the hip fracture cases across the world will occur in Asia. Given the demographics of the aging population, the prevalence of this condition is anticipated to progressively rise in the coming years\(^3\). In Europe and North America, the prevalence, prognosis, and financial burden are associated with FF are equivalent to or even exceed those of major cardiovascular diseases\(^2\).

Socio-economic status (SES) is a striking and all-embracing concept that reflects place of an individual within a hierarchical social structure, primarily assessed in terms of factors such as income, education, and levels of material deprivation\(^4\). SES-related factors are acknowledged as primary causes of both acute and chronic diseases, including conditions such as osteoporosis and FF\(^5\). These factors directly impact various disease outcomes, and indirectly affect multiple
risk factors associated with outcomes of diseases, even shaping the configuration of health
resources. The latest conceptualizations of diversions also posit that insufficient attention to
advantaged groups, compared with disadvantaged groups, may lead to an incomplete
exploration of health inequality sources. A diversity of observational retrospective studies has
consistently demonstrated a higher prevalence of osteoporosis among adult individuals with
lower levels of educational attainment, unemployment, and lower income. Interestingly,
according to the study by Gough Courtney M et al., higher childhood SES or greater maternal
investment can also reduce the probability of osteoporosis diagnosis. Nevertheless, recent
years have witnessed the emergence of conflicting evidence. Elliot et al. revealed a negative
association between SES and BMD in Caucasian male population. Subsequently, a cohort
study reported no discernible association between SES and wedge deformities in females, even
when comparing those at extreme social disadvantage to their wealthier counterparts.
Meanwhile, it remains uncertain if income, education, and material deprivation independently
contribute to osteoporosis and fractures. A systematic review also highlights that while a
few limited yet well-conducted studies suggest an association between SES and the risk of
osteoporosis, further research is needed to substantiate these findings. Addressing socio-
economic disparities in osteoporosis and fractures necessitates a comprehensive understanding
of the underlying mediating mechanisms. While some studies have hypothesized that
individuals with obesity and diabetes face a reduced risk of osteoporosis compared to those
without these conditions, other findings suggest that elevated BMI levels may confer a
protective effect against osteoporosis.
Research on cohorts to answer the questions listed above necessitates an extended follow-up period, which is undoubtedly laborious and time-consuming. Besides, observational studies are hypersensitized to confounding factors and reverse causality, which can hinder the establishment of causal relationships.

Given these numerous issues, an innovative epidemiological approach known as Mendelian Randomization (MR) has been much applied for this need to address these problems. It has been widely used to infer the causal relationship between the exposure and outcome in academic research for its relative advantage of exploiting genetic variants as instrumental variables (IVs). This is determined at the start and naturally randomized among individuals, largely to minimize the impact of confounding factors and the bias associated with reverse causation. Multivariable Mendelian Randomization (MVMR) is an extension of MR, which enables a comparable mediation analysis. Compared to traditional observational studies, these kinds of research approaches are more productive and valuable in providing credible evidence.

Hence, we conducted a bidirectional MR study to explore the causal effects between SES and osteoporosis and fractures. We aimed to contribute new empirical insights to this association to potentially add value to future screening, surveillance initiatives, and public health policy decisions.

**Materials and Methods**

**Study design**
We selected three representative SES traits based on prior investigations, including years of schooling completed, average total household income before tax, and Townsend Deprivation Index at recruitment. We performed a bidirectional MR analysis using summary statistics from genome-wide association studies (GWAS) to analyze the causal relationship of SES-related factors with osteoporosis and the five most common fracture phenotypes of the spine, femur, ankle, foot, and wrist. Our study adheres to the reporting guidelines outlined in the strengthening the reporting of observational studies in epidemiology using mendelian randomization (STROBE-MR) statement\(^{(21)}\). Figure 1 presents the flowchart of our MR design.

**Data sources**

We intentionally attempted to select samples from separate databases to mitigate the risk of inflated type I error rates due to potential participant overlap between exposure and outcome samples \(^{(22)}\). It is worth mentioning that all cases and controls in these studies had a shared European ancestry.

Genome-Wide Association Study data for socioeconomic status-related factors

We obtained genetic associations of education from the Social Science Genetic Association Consortium (SSGAC): a GWAS of years of schooling completed and published in 2018. It is one of the most widely utilized databases for educational research, involving 1,131,881 individuals of European ancestry. The MRC IEU OpenGWAS database, developed at the MRC Integrative Epidemiology Unit at the University of Bristol, was the source of single-nucleotide polymorphisms (SNPs) strongly associated with income and material deprivation. This is given
the substantial sample size and reliability of the database, which can be accessed at
https://gwas.mrcieu.ac.uk. Detailed information for each phenotype is presented in Table 1.

Genome-Wide Association Study data for osteoporosis, bone mineral density, and fractures

We acquired the GWAS statistical summary for osteoporosis from the recently published 2023
dataset of the FinnGen study (accessed at https://r9.finngen.fi/). We obtained data on BMD to
indirectly assess the causal effect of SES on osteoporosis through MR analysis, providing
additional verification of our results. GWAS summary statistics for BMDs (unit: g/cm²) were
acquired from the Genetic Factors for Osteoporosis Consortium (GEFOS;
http://www.gefos.org/). Furthermore, given that fractures are the most profound complication
associated with osteoporosis and are an indirect measure of its seriousness, the various sites of
fracture sites are the outcomes in our MR study. We selected GWAS summary statistics from
FinnGen R9 study for five fracture sites, including the spine, femur, lower leg-ankle, foot, and
wrist-hand. We examined the causal effect of SES on fractures to obtain more comprehensive
conclusions. There was no sex heterogeneity in all GWAS datasets. The details of these data
sources including consortium, ancestry, sample size and sex ratio were provided in Table 1.

Osteoporosis and fractures were defined based on the occurrence of one or more International
Classification of Disease, 10th Revision (ICD10) codes (Supplementary Table S1).

Selection of genetic variants

In the MR analysis, IVs must meet the following three basic assumptions to obtain robust
conclusions\(^{23}\): I) Relevance: IVs are strongly associated with the exposure; II) Independence:
there is no correlation between IVs and confounders; III) Exclusion restriction: IVs affect the
outcome only through the exposure. We implemented a series of quality control measures following these main assumptions to select instrumental SNPs. At the initial stage, SNPs were required to exhibit significant associations with the corresponding exposure, and reached a genome-wide significance level ($P < 5 \times 10^{-8}$). Subsequently, we removed SNPs in linkage disequilibrium (LD) by pruning with $R^2 < 0.001$ and a window size of 10,000 kb. Next, we retrieved data for the chosen SNPs from the GWAS summary statistics of the eight outcomes. This selection process mandated a minor allele frequency (MAF) exceeding 0.01. We computed the F-statistic with the formula: $F = R^2(N - 2) / (1 - R^2)$ to assess the presence of weak instrumental variable bias. Here, we literally checked if the genetic variants chosen as instrumental variables exhibited a weak association with the exposure. Notably, SNPs with F-statistics $< 10$, along with ambiguous and palindromic SNPs, were directly excluded during the reconciliation of exposure and outcome effects. Finally, we identified and eliminated SNPs exhibiting potential horizontal pleiotropy by utilizing MR-pleiotropy residual sum and outlier (MR-PRESSO). In the subsequent MR analysis, these meticulously screened SNPs served as valid IVs, ensuring the integrity and reliability of our analysis. The SNPs used as IVs are comprehensively described in Supplementary Table S2-S12.

Mendelian randomization estimates: univariable and multivariable Mendelian randomization analysis

Our primary analysis entailed the application of the inverse-variance weighted (IVW) MR method. This method computes the weighted average of Wald ratios across SNPs based on the SNP-exposure beta coefficients. The IVW method assumes the validity of all instruments or
balanced pleiotropy. The IVW linear regression provides an unbiased causal estimate in the absence of horizontal pleiotropy or when pleiotropy is balanced\(^\text{26}\). Both fixed and random-effects IVW approaches were employed for analyses. We chose fixed-effects IVW when there was no heterogeneity, while a random-effect IVW model was applied in cases where significant heterogeneity (\(P < 0.05\)) was detected. We performed MR-PRESSO to address concerns of horizontal pleiotropy and to remove outliers with 10,000 permutations to ensure convincing results\(^\text{25}\). Furthermore, we incorporated two supplementary detection methods in our MR analysis: the weighted median and MR-Egger. The MR-Egger was expected to yield an unbiased estimation of the causal effect even if all SNPs exhibited pleiotropy but remained independent of the exposure association\(^\text{27}\). Though the weighted median method accommodated the inclusion of up to 50\% of potentially invalid SNPs due to pleiotropy, it has consistently provided reliable estimates\(^\text{28}\).

Furthermore, we performed additional MVMR analyses to address potential pleiotropic effects of several risk factors associated with lifestyle\(^\text{29}\). These included body mass index (BMI), smoking initiation, alcohol intake frequency, and type 2 diabetes. The detailed information for these confounders has been presented in Table 1.

Mendelian randomization sensitivity analysis

We assessed SNP heterogeneity using Cochran's Q test with a \(P\)-value \(< 0.05\) as indicative of potential heterogeneity in the sensitivity analysis. We examined the deviation of the intercept from zero as a measure of horizontal pleiotropy, with \(P < 0.05\) in the MR-Egger regression. Additionally, we conducted a leave-one-SNP-out analysis to judge the impact of individual
variants on the outcome and generated funnel plots to visualize the results. We also investigated whether the genetic instruments were linked to other relevant traits (P < 5×10⁻⁸) using Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/). We corroborated the causal relationships between exposures and outcomes using the IVW method after the exclusion of SNPs associated with BMI, type 2 diabetes, smoking, and alcohol intake. We corroborated the causal relationships between exposures and outcomes using the IVW method after the exclusion of SNPs associated with BMI, type 2 diabetes, smoking, and alcohol intake.

The statistical power was calculated using an online tool (https://sb452.shinyapps.io/power/), given a type I error of 5% (Supplementary Table S13-14). We used a Benjamini–Hochberg false discovery rates (FDR) correction to account for multiple testing. P-values below 0.05 that did not withstand the FDR correction were regarded as indicative of a potential association. The MR estimates were presented as odds ratios (ORs), β coefficients, or proportions, each with their corresponding 95% confidence intervals (CIs).

Our statistical analysis used the two-sample MR package (version 0.5.6), MR-PRESSO package (version 1.0), and MendelianRandomization package (version 0.7.0) in the R program (version 4.3.0; R Foundation for Statistical Computing, 2023). It is important to note that our study exclusively utilized summary-level statistics, which circumvented the need for ethical approval.

Results
We assessed the strength of our genetic instruments using the F-statistic, which exceeded 10 for all SNPs used in the MR analysis, indicating the absence of weak instrument bias.
A visual representation of our leave-one-out analysis and funnel plots for all estimates, is presented in Supplementary Figure S1-S5.

UVMR estimates for the bidirectional causal association between socio-economic status and osteoporosis and bone mineral density

The initial MR estimates obtained from various methods assessing the causal influence of SES-related factors on osteoporosis, revealed a negative association between educational attainment and osteoporosis incidence (IVW: odds ratio [OR]: 0.78, 95% confidence interval [CI]: 0.65-0.94, \(P = 8.49 \times 10^{-3}\)), as displayed in Table 2 and Figure 2. Even after applying FDR correction, this causal effect remained significant, with an adjusted \(P\)-value of 0.02547. Further, given that MR-PRESSO detected no outliers, the robustness of the result was ascertained (OR: 0.78, 95% CI: 0.65-0.94, \(P = 8.95 \times 10^{-3}\)). Furthermore, we observed a more stable causality (OR: 0.70, 95% CI: 0.57-0.87, \(P = 1.01 \times 10^{-3}\)) after screening 49 SNPs associated with other traits like BMI, height, type 2 diabetes, smoking habits, and alcohol intake frequency, and repeating the MR analysis. Our analysis found no significant evidence of horizontal pleiotropy, as indicated by the MR-Egger regression intercept, which is close to zero with a \(P\)-value larger than 0.05. Given that the Cochran's Q statistic (Q value = 352.40, \(P = 0.0088\)) suggested moderate heterogeneity, we mainly used the random-effects IVW as the method of analysis. Leave-one-out analysis confirmed that the estimated effects did not depend on specific SNPs (refer to Supplementary Figure S1). The IVW model, however, indicated no causal effect of household income and material deprivation on osteoporosis in this context. Interestingly, income emerged as a protective factor against osteoporosis (OR: 0.52, 95% CI: 0.31-0.87, \(P = 0.0122\), when
employing the weighted median (OR: 0.56, 95% CI: 0.35-0.91, P = 0.0198) and IVW methods
omitted corresponding confounders. This observation suggested the potential impact of income
on osteoporosis, which warrants further investigation in future research.

We chose two types of BMD commonly used for diagnosing and broadly screening
osteoporosis femoral neck bone mineral density (FN-BMD) and heel bone mineral density
eBMD), respectively for the replication analysis. The results showed a robust causal
relationship between education and eBMD after the removal of 12 outliers (IVW: beta: 0.06,
95% CI: 0.01-0.10, P = 7.24×10^{-3}, adjusted P = 0.0248; weighted median: beta: 0.05, 95% CI:
0.00-0.11, P = 0.0461; MR-PRESSO: beta: 0.06, 95% CI: 0.01-0.10, P = 7.66×10^{-3}). These
results are shown in of Table 2 and were consistent with our primal analyses. Given that the
MR analyses of educational attainment on eBMD had some heterogeneity but no pleiotropy,
we employed the random-effects IVW method to assess causality and found no significant
association between income, deprivation, and eBMD. Furthermore, our analysis did not reveal
a causal effect of SES-related factors on FN-BMD in this regard, except for the IVW results of
the Townsend Deprivation Index at recruitment, which showed a modest association after
controlling for confounders (with criteria as mentioned above). Considering all of our results,
there was a causal effect of genetically proxied educational attainment (not implying education
level is controlled by genetics) on osteoporosis and eBMD, but not on FN-BMD. Besides, after
excluding SNPs related to confounding factors, the unassuming casual effect appeared between
income on osteoporosis and deprivation on eBMD, supporting the significant and possible roles
of the risk factors as mediators in these relationships.
We also detected the causal effect of osteoporosis and BMD on SES (Supplementary Table S15-S16). An elevated score of FN-BMD was associated with a higher income level (IVW: beta: 0.03, 95% CI: 0.01-0.04, P = 6.78×10^{-3}, adjusted P = 0.0163; weighted median: beta: 0.03, 95% CI: 0.00-0.05, P = 0.0376; MR-PRESSO: beta: 0.03, 95% CI: 0.01-0.04, P = 3.07×10^{-3}).

Notably, the observed causality persisted even after excluding 9 SNPs associated with other traits, such as BMI. Moreover, we found no statistically significant effect of osteoporosis and eBMD on SES when FDR correction was applied. We did not detect any horizontal pleiotropy or heterogeneity in rigorous sensitivity analyses, as confirmed by the MR-Egger intercept test and Cochran’s Q statistic (as shown in Supplementary Table S1).

UVMR estimates for the bidirectional causal association between socio-economic status and fractures

We subsequently selected GWAS data from various fracture sites to investigate whether SES-related factors also exhibited a causal relationship with fractures. This approach not only represented further analysis but also served as additional verification of the influence of SES on osteoporosis. In this regard, educational attainment would be a protective factor against all types of fractures listed. To elaborate, spine fracture: OR: 0.76, 95% CI: 0.66-0.88, P = 2.93×10^{-4}, adjusted P = 0.00352; femur fracture: OR: 0.78, 95% CI: 0.67-0.91, P = 1.33×10^{-3}, adjusted P = 0.0106; lower leg-ankle fracture: OR: 0.79, 95% CI: 0.70-0.88, P = 2.05×10^{-5}, adjusted P = 4.92×10^{-4}; foot fracture: OR: 0.78, 95% CI: 0.66-0.93, P = 5.92×10^{-3}, adjusted P = 0.0248; wrist-hand fracture: OR: 0.83, 95% CI: 0.73-0.95, P = 7.15×10^{-3}, adjusted P = 0.0248 (Table 3). While Townsend Deprivation Index at recruitment exerted a deleterious effect on
spine fracture (OR: 2.63, 95% CI: 1.43-4.85, P = 1.91×10⁻³, adjusted P= 0.0115) and femur fracture (OR: 1.98, 95% CI:1.06-3.73, P = 0.0332, adjusted P = 0.0885), the statistical significance for femur was lost after FDR correction, making us cautiously interpret the result.

Regarding the estimates for bidirectional causal associations, the IVW method revealed that the impact of foot fracture on income was minimally significant. However, this statistical significance was lost upon employing FDR correction. All these MR analyses did not exhibit significant pleiotropy, and we chose fixed-effects IVW when there was no heterogeneity; instead, a random-effect IVW model was applied (Table 4 and Supplementary Table S16-S17).

MVMR estimates for bidirectional causal associations between socio-economic status and osteoporosis, bone mineral density and fractures

In light of the presence of confounding factors (BMI, type 2 diabetes, smoking and alcohol intake frequency), we proceeded with MVMR to identify the independent influence of the exposure. This measurement was conducted during the results with a significant P-value observed in the UVMR analysis after FDR correction. After accounting for BMI and alcohol as individual confounders, a robust causal relationship between education and osteoporosis, and all fracture types persisted. Townsend Deprivation Index at recruitment remained causally linked to a higher risk of spine fracture. Notably, the protective influence of educational attainment on foot fracture diminished in the presence of diabetes and smoking. Furthermore, our MVMR analysis indicated that smoking may play a pivotal role in mediating the effect of educational attainment on eBMD levels, foot fracture, and wrist-hand fracture (Figure 3).
Moreover, a discernible causal effect of FN-BMD on income was evident after adjustments for BMI and smoking. However, this effect diminished upon further adjustments for diabetes and alcohol (as shown in Supplementary Table S1).

Discussion

Osteoporosis is frequently referred to as a "silent" disease since patients typically do not show evident symptoms until the occurrence of fractures. This silent nature of bone disease often results in its neglect, leading to insufficient focus on preventive measures. Currently, the prevention of osteoporosis and its associated complications remains a significant challenge.

While extensive research has delved into the underlying biomolecular mechanisms, a notable gap exists in our understanding of the causal relationships between SES-related phenotypes and osteoporosis. To formulate practical strategies for osteoporosis prevention in this work, we employed a bidirectional MR design to investigate the potential causal links between average total household income before tax, years of schooling completed, Townsend Deprivation Index at recruitment, and osteoporosis, FN-BMD, eBMD, and fractures at five distinct sites, and adjusted for four primary confounding factors using MVMR analysis. Our findings shed light on the critical roles played by educational attainment and material deprivation in osteoporosis development and fractures and pointed out the protective role of FN-BMD in the household income.

It is widely acknowledged that household income, educational attainment and deprivation are reliable indicators of SES. Numerous studies have elucidated the intricate connection between
socio-economic disparities and a spectrum of chronic diseases, such as diabetes\(^{34}\), inflammatory bowel disease\(^{35}\), and many of cancer types\(^{36,37}\). Osteoporosis is an age-related chronic ailment that been extensively linked to a multitude of modifiable risk factors, including obesity, tobacco smoking, alcohol consumption, and psychological factors like stress and depression. More importantly, several conventional epidemiological studies have hinted at a correlation between osteoporosis development and SES, including access to healthcare and other resources\(^{38}\). However, these findings have been limited by conflicting conclusions due to challenges, such as modest sample sizes, challenges related to reverse causality, and an inability to comprehensively control for confounding variables. For instance, Brennan et al. presented a significant negative trend in the relative risk of osteoporotic fractures for the lowest versus highest income quintile, with a relative risk of 1.63 (95% CI: 1.42-1.87) among Canadian men\(^{39}\). Similarly, another study found a heightened risk of osteoporosis within low-income (OR: 1.90, 95% CI: 1.07-3.37) and food-insecure (OR: 3.48, 95% CI: 1.43-8.48) among Portuguese populations\(^{40}\). The same conclusion has been drawn by studies published in 2019\(^{10}\) and 2021\(^{16}\). Several studies have predicted a negative association of SES with fracture risk\(^{41,42}\). However, a study on 17,155 women (aged 65-81 years) found no disparities in the risk of osteoporotic fractures based on SES\(^{43}\). Meanwhile, an observational study conducted in the United Kingdom suggested that socio-economic deprivation did not appear to be a risk factor for developing osteoporotic fractures in elderly individuals\(^{44}\). Given that the effect of confounders, such as BMI and diabetes, on osteoporosis remained undefined, scholars have proposed different hypotheses\(^{(19,45)}\).
To address these aforementioned problems, we designed a bidirectional MR analysis to explore the causal effect of SES-related factors on osteoporosis and fractures. Our findings align with previous MR studies that have consistently demonstrated the protective role of higher education. Notably, we observed that among socio-economic factors, education, instead of income or deprivation, exerted the predominant influence on osteoporosis, eBMD, and fractures across five sites. Each one-s.d. increase (4.20 years) in genetically proxied education level was causally associated with 22%, 24%, 22%, 21%, 22%, and 17% decreased risk of osteoporosis, spine fracture, femur fracture, lower leg-ankle fracture, foot fracture, and wrist-hand fracture, respectively. Earlier reports also indicated that higher SES in both adult stages and childhood was associated with a reduced prevalence of osteoporosis that aligned with our current findings\cite{11,12,43}. Moreover, given that IVs related to education were randomly distributed and determined at conception, they may serve as a key predictor of osteoporosis risk across the lifespan. This highlights the potential of education as a sensitive marker for early osteoporosis detection. Our MR outcomes are reasonable considering the modern socio-economic landscape inclusive of diverse income sources, leading to significant variability in educational attainment even in high-income individuals. Notably, educational attainment has emerged as a focal point of contemporary academic research, given its potential as a robust defense against many diseases\cite{46,47}. In this regard, firstly, education can partially determine further wealth accumulation. Secondly, higher educational attainment can signify broader access to social resources, such as the enhanced economic capacity to afford medical care, awareness to seek superior healthcare facilities, and improved healthcare knowledge, for instance, maintaining
physique through regular proactive exercise. These factors are conducive to early identification of reduced BMD, enabling proactive measures such as the increased intake of calcium and Vitamin D. Additionally, our findings also underscore the importance of conducting routine BMD testing and osteoporosis screening in community settings, particularly in economically disadvantaged areas. There is a clear need to augment the dissemination of osteoporosis-related information and promote awareness regarding early detection of this condition.

Interestingly, socio-economic factors did not appear to significantly influence FN-BMD, suggesting that these factors may have distinct effects at different skeletal sites. The human adult skeleton is comprised of approximately 80% cortical bone and 20% trabecular bone. However, the ratios of cortical to trabecular bone vary at various bones and skeletal sites, for instance, long bones have a higher ratio of cortical to trabecular bone. Typically, cortical bone is less metabolically active than trabecular bone, and as individuals age, they often experience cortical thinning and increased cortical porosity, which can lead to reduced bone strength. This variation of impact on different bone types may be attributed to differences in mineral metabolism levels that are influenced by the nutritional status associated with SES. However, it is important to note that while the individual effects on bone density may appear modest, the cumulative impact of these factors over time can contribute to the development of osteoporosis.

Very few studies have focused on the effects of BMD on SES. Our bidirectional MR results demonstrated that an augmentation in FN-BMD had a protective influence on average total household income before tax, consistent with the prior studies. Elevated bone density often indicates diminished fracture incidence, improved individual health, and an enriched quality of life.
life. All these factors positively contribute to the household income. Intriguingly, our data suggested that occurrences of fractures in different body regions do not yield statistically significant effects on SES. This may be attributed to our utilization of average total household income before tax as a comprehensive metric, wherein the degree of reduction in household income is less pronounced than individual income loss. When one family member suffers from a broken bone, other members augment their labor involvement to mitigate the natural smoothing effect stemming from the patient’s income decline. Moreover, the substantial sample size comprising diverse European populations from varied regions in this study may give rise to regional disparities in social welfare, potentially contributing to negative causal relationships. Consequently, exploring variations in individual and household income after fractures in different body parts based on genetic predictions is imperative for future research.

To the best of our knowledge, our study was the first MR-based analysis exploring the causal relationships between SES and osteoporosis and its complications. Previous studies are limited to one outcome usage, lack of the assessment of direction, and absence of adjustment to a few risk factors. In our study, we selected three phenotypes representing the risk of osteoporosis and analyzed five different fracture sites using five different methods. This allowed us to obtain refined conclusions, minimize sample overlap, and incorporate replication analyses to ensure robust results. Moreover, we chose lifestyle-related confounders based on the epidemiology of osteoporosis and fractures to conduct the MVMR study to explain the independent effect of the exposures to a certain extent.
Several limitations in our MR analysis warrant consideration. Firstly, our study exclusively focused on individuals of European ancestry, signifying that the generalizability of our findings to racially and ethnically diverse populations need to approach with caution. More diverse cohorts are needed to investigate the associations between SES and osteoporosis and fractures across worldwide populations. Secondly, MR analyses are susceptible to potential bias stemming from horizontal pleiotropy, where genetic variants influence outcomes through pathways unrelated to the investigated exposure. However, the MR-Egger intercept analysis provided limited indications of pleiotropy in most associations, so the results in this study are acceptable. Thirdly, each method employed in our analysis has its unique strengths and weaknesses, which could not be avoided in the MR analysis, urging us to conclude the results carefully and comprehensively.

Conclusion

In conclusion, our analysis provides compelling evidence indicating that higher education attainment is associated with higher eBMD, reduced risk of osteoporosis and fractures, while material deprivation is related to increased risk of spine fracture. Further, it is suggested that promoting the FN-BMD score may help to increase the household income. These findings offer valuable insights for developing health strategies and policies and underscore the significance of regular BMD surveillance in communities, particularly in economically disadvantaged areas. Additionally, efforts focused on increasing knowledge and awareness among individuals to promote bone health and fracture prevention are warranted for a healthy society.
Data availability statement

All relevant data for the study are either included in the article or provided as supplemental information.

Acknowledgements & Funding

This work was supported by the National Natural Science Foundation of China (No.82370892, 82070910, 82100944 and 82100494), National Key Research & Development Program (No.2021YFC2501701), the Health Research Project in Hunan Province (No.20231696), the Natural Science Foundation of Hunan Province (No.2022J40721) and the Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University (No.7673). The authors acknowledge the consortia for their efforts in providing researchers with high-quality GWAS resources. This article does not contain any studies with human or animal subjects. Figures were created with biorender.com.

Author contributions

Jia-Yue Duan: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review&editing. Rui-Xuan You: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review&editing. Yong Zhou: Formal analysis; Methodology; Software; Validation. Feng Xu: Methodology; Validation; Visualization. Xiao Lin: Formal analysis; Methodology; Validation; Visualization. Su-Kang Shan: Methodology; Supervision;
Validation; Visualization. **Ming-Hui Zheng**: Methodology; Software; Supervision; Validation.

**Li-Min Lei**: Data curation; Investigation; Methodology; Validation. **Fu-Xing-Zi Li**: Conceptualization; Methodology; Validation; Writing - original draft. **Bei Guo**: Formal analysis; Methodology; Software; Supervision; Validation. **Yun-Yun Wu**: Conceptualization; Methodology; Validation; Visualization. **Xi Chen**: Software; Validation; Visualization. **Ke-Xin Tang**: Methodology; Validation; Visualization. **Ye-Chi Cao**: Formal analysis; Methodology; Validation; Visualization. **Si-Yang He**: Methodology; Supervision; Validation; Visualization. **Yan-Lin Wu**: Software; Supervision; Validation; Visualization. **Rong Xiao**: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Writing - original draft; Writing - review&editing. **Ling-Qing Yuan**: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Writing - original draft; Writing - review&editing.

**Conflicts of Interest**

The authors have declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
References


Legends for Figures and Tables

Figure 1. Flowchart of the current MR design.
Figure 2. Visualized results of the analysis. All results described here can be found in Table 1-3.
Figure 3. MVMR estimates for SES on osteoporosis and fractures during the results with significant P-value observed in the UVMR analysis following FDR correction.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>SNP</th>
<th>OR (95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>osteoporosis</td>
<td>269</td>
<td>0.71(0.52-0.96)</td>
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<tr>
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<td>femur fracture</td>
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<tr>
<td>education</td>
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<td>wrist fracture</td>
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<td>0.10(0.04-0.29)</td>
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</tr>
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<tr>
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<td>eBMD</td>
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<td>0.12(0.24-0.61)</td>
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<td>education</td>
<td>femur fracture</td>
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</tr>
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<td>education</td>
<td>wrist fracture</td>
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<tr>
<td>MVMR Model 5 (adjusting for adjusted for BMI, diabetes, alcohol and smoking)</td>
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## Table 1. GWAS datasets in the mendelian randomization study.

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<tr>
<th>Phenotype</th>
<th>Unit</th>
<th>Consortium</th>
<th>Ancestry</th>
<th>Sample size</th>
<th>Fraction female</th>
<th>Year of publication</th>
<th>PMID</th>
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<td></td>
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<td></td>
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<tr>
<td>Average total household income before tax</td>
<td>s.d.</td>
<td>MRC-IEU</td>
<td>European</td>
<td>397,751</td>
<td>0.54</td>
<td>2018</td>
<td>NA</td>
</tr>
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<td>Years of schooling completed</td>
<td>1 s.d. (4.20 years)</td>
<td>SSGAC</td>
<td>European</td>
<td>1,131,881</td>
<td>0.55</td>
<td>2018</td>
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<td>Townsend Deprivation Index at recruitment</td>
<td>s.d.</td>
<td>MRC-IEU</td>
<td>European</td>
<td>462,464</td>
<td>0.54</td>
<td>2018</td>
<td>NA</td>
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<td><strong>Confounder</strong></td>
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<td>Body Mass Index</td>
<td>s.d.</td>
<td>MRC-IEU</td>
<td>European</td>
<td>454,884</td>
<td>0.54</td>
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<td>Type 2 diabetes</td>
<td>Event</td>
<td>Meta</td>
<td>European</td>
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<td>0.54</td>
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<td>Smoking initiation</td>
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<td>European</td>
<td>607,291</td>
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<td>Alcohol intake frequency</td>
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<td></td>
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<tr>
<td>Phenotype of Osteoporosis</td>
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<td>Osteoporosis</td>
<td>Event</td>
<td>Finngen</td>
<td>European</td>
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<tr>
<td>\textit{FN-BMD}</td>
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<td>GEFOS</td>
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<td>32,735</td>
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<td>\textit{eBMD}</td>
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<td>2017</td>
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<td>Spine Fracture</td>
<td>Event</td>
<td>Finngen</td>
<td>European</td>
<td>371,354</td>
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<tr>
<td>Fracture Event</td>
<td>Source</td>
<td>Population</td>
<td>Sample Size</td>
<td>MAF</td>
<td>Year</td>
<td>Study Code</td>
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<tr>
<td>Femur Fracture</td>
<td>FinnGen</td>
<td>European</td>
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<td>Lower Leg-ankle Fracture</td>
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<tr>
<td>Wrist-Hand Fracture</td>
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<td>2023</td>
<td>36653562</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GWAS, genome-wide association study; SSGAC, Social Science Genetic Association Consortium; MRC-IEU, Medical Research Council-Integrative Epidemiology Unit; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; GEFOS, Genetic Factors for Osteoporosis Consortium; FN-BMD, femoral neck bone mineral density; eBMD, bone mineral density from quantitative heel ultrasounds.

a Although this dataset did not provide specific sex composition ratio, the ratio of male to female was comparable according to the description of the original literature.
Table 2. Mendelian randomization estimates for the associations between three phenotypes of socio-economic status and different reflects of osteoporosis.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Method</th>
<th>No. of SNPs or outliers</th>
<th>Beta (95% CI)</th>
<th>OR (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
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<td>Average total household income before tax</td>
<td>Osteoporosis</td>
<td>IVW</td>
<td>-</td>
<td>0.73 (0.50, 1.07)</td>
<td>0.56 (0.35, 0.91)</td>
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<tr>
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<td>0.52 (0.31, 0.87)</td>
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<tr>
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<td>-</td>
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<td>0.50 (0.07, 3.76)</td>
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<td>-</td>
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<td></td>
<td>-</td>
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<td>0.80 (0.62, 1.03)</td>
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<tr>
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<td>-</td>
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<td>Osteoporosis</td>
<td>IVW</td>
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<td>0.78 (0.65, 0.94)</td>
<td>0.99 (0.49, 1.99)</td>
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<td>1.01×10^-3</td>
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<td>17</td>
<td>-</td>
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<td>1.11 (0.44, 2.83)</td>
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<td>MR Egger</td>
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<td>-</td>
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<td>11.30 (0.19, 675.05)</td>
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</tr>
<tr>
<td>MR-PRESSO</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
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<td>1.17 (0.49, 2.78)</td>
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<td>Variable</td>
<td>Method</td>
<td>Estimate</td>
<td>95% CI</td>
<td>p-value</td>
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<td></td>
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<td>-------------------------------------------------</td>
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<td></td>
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</tr>
<tr>
<td>Average total household income before tax</td>
<td>IVW</td>
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<tr>
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<tr>
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<td>-</td>
<td>0.164</td>
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<tr>
<td></td>
<td>IVW(without cofounders)</td>
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<td>MR Egger</td>
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<td>0.04(-0.18,0.26)</td>
<td>-</td>
<td>0.707</td>
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<td>IVW</td>
<td>0.06(-0.02,0.13)</td>
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<td>-</td>
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<td>0.05(-0.04,0.14)</td>
<td>-</td>
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<td>IVW</td>
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<td>-0.29(-0.59,0.00)</td>
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<td>0.0721</td>
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<td>IVW</td>
<td>0.04(-0.11,0.18)</td>
<td>-</td>
<td>0.619</td>
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<td>Weighted median</td>
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<td>-</td>
<td>0.711</td>
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<td>IVW(without cofounders)</td>
<td>-0.58(-1.05,-0.10)</td>
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<td>0.0173</td>
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**Note:** The 95% CI values are presented as (-lower bound, upper bound).
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<th>MR Egger</th>
<th>MR-PRESSO</th>
<th>IVW(without cofounders)</th>
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<td>0.08(-0.09,0.24)</td>
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<td>0.07(0.00,0.11)</td>
<td>0.06(0.01,0.10)</td>
<td>0.03(-0.02,0.08)</td>
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<td>0.07(0.00,0.11)</td>
<td>0.06(0.01,0.10)</td>
<td>0.03(-0.02,0.08)</td>
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<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td>Weighted median</td>
<td>MR Egger</td>
<td>MR-PRESSO</td>
<td>IVW(without cofounders)</td>
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<td>0.07(0.00,0.11)</td>
<td>0.06(0.01,0.10)</td>
<td>0.03(-0.02,0.08)</td>
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</table>

Abbreviations: FN-BMD, femoral neck bone mineral density; eBMD, bone mineral density from quantitative heel ultrasounds; CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; MR, mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier.

a. Betas are presented for the analyses of continuous/ordinal outcomes.

b. OR are presented for the analyses of binary/dichotomous outcomes.

c. The numbers of SNPs used as IVs in the IVW, weighted median and MR Egger methods and the number of outliers identified and excluded in the MR PRESSO method.

d. P < 0.05 was considered significant.
Table 3. Mendelian randomization estimates for the associations between three phenotypes of socio-economic status and five types of fracture.

<table>
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<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Method</th>
<th>No. of SNPs or outliers</th>
<th>OR(95% CI)</th>
<th>P value</th>
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<td>Average total household income before tax</td>
<td>Spine Fracture</td>
<td>IVW</td>
<td>0.89(0.67,1.17)</td>
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<td>Weighted median</td>
<td>1.11(0.74,1.69)</td>
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<td>0.78(0.62,0.97)</td>
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<td>0.76(0.66,0.89)</td>
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<td>IVW(without cofounders)</td>
<td>0.73(0.61,0.86)</td>
<td>2.13×10^{-4}</td>
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<td>IVW</td>
<td>2.63(1.43,4.85)</td>
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<tr>
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<td>IVW(without cofounders)</td>
<td>3.00(1.39,6.47)</td>
<td>4.95×10^{-3}</td>
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<td>Variable</td>
<td>IVW</td>
<td>Weighted median</td>
<td>MR Egger</td>
<td>MR-PRESSO</td>
<td>IVW(without cofounders)</td>
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<tr>
<td><strong>Average total household income before tax</strong></td>
<td>0.87(0.65,1.16)</td>
<td>0.97(0.63,1.49)</td>
<td>2.31(0.47,11.34)</td>
<td>0.87(0.64,1.19)</td>
<td>0.56(0.35,0.90)</td>
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<td><strong>IVW</strong></td>
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<tr>
<td><strong>Weighted median</strong></td>
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<td><strong>IVW(without cofounders)</strong></td>
<td>0.56(0.35,0.90)</td>
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<tr>
<td><strong>Years of schooling completed</strong></td>
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<td>0.73(0.58,0.91)</td>
<td>0.90(0.49,1.66)</td>
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<tr>
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<td><strong>Townsend Deprivation Index at recruitment</strong></td>
<td>1.98(1.06,3.73)</td>
<td>1.77(0.70,4.42)</td>
<td>14.11(0.28,708.45)</td>
<td>1.98(1.03,3.84)</td>
<td>2.83(1.28,6.25)</td>
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<td><strong>Femur Fracture</strong></td>
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<tr>
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<td><strong>MR Egger</strong></td>
<td>14.11(0.28,708.45)</td>
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<tr>
<td><strong>IVW(without cofounders)</strong></td>
<td>2.83(1.28,6.25)</td>
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<tr>
<td><strong>Average total household income before tax</strong></td>
<td>1.98(1.06,3.73)</td>
<td>1.77(0.70,4.42)</td>
<td>14.11(0.28,708.45)</td>
<td>1.98(1.03,3.84)</td>
<td>2.83(1.28,6.25)</td>
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<tr>
<td><strong>Lower leg-ankle Fracture</strong></td>
<td>0.93(0.74,1.17)</td>
<td>0.93(0.74,1.17)</td>
<td>1.24(0.38,4.06)</td>
<td>0.93(0.74,1.17)</td>
<td>0.98(0.72,1.33)</td>
</tr>
<tr>
<td><strong>Weighted median</strong></td>
<td>1.06(0.79,1.41)</td>
<td>1.06(0.79,1.41)</td>
<td>1.24(0.38,4.06)</td>
<td>0.93(0.74,1.17)</td>
<td>0.98(0.72,1.33)</td>
</tr>
<tr>
<td><strong>MR Egger</strong></td>
<td>1.24(0.38,4.06)</td>
<td>1.24(0.38,4.06)</td>
<td>0.72(0.35,1.49)</td>
<td>0.93(0.74,1.17)</td>
<td>0.98(0.72,1.33)</td>
</tr>
<tr>
<td><strong>MR-PRESSO</strong></td>
<td>0.93(0.74,1.17)</td>
<td>0.93(0.74,1.17)</td>
<td>1.24(0.38,4.06)</td>
<td>0.93(0.74,1.17)</td>
<td>0.98(0.72,1.33)</td>
</tr>
<tr>
<td><strong>IVW(without cofounders)</strong></td>
<td>0.98(0.72,1.33)</td>
<td>0.98(0.72,1.33)</td>
<td>1.24(0.38,4.06)</td>
<td>0.93(0.74,1.17)</td>
<td>0.98(0.72,1.33)</td>
</tr>
<tr>
<td>Variable</td>
<td>Method</td>
<td>Estimate</td>
<td>95% CI</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>--------</td>
<td>----------</td>
<td>--------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>IVW</td>
<td>0.79</td>
<td>(0.70, 0.88)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>0.73</td>
<td>(0.62, 0.86)</td>
<td>0.003</td>
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<tr>
<td></td>
<td>MR Egger</td>
<td>0.80</td>
<td>(0.52, 1.22)</td>
<td>0.301</td>
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<tr>
<td></td>
<td>MR-PRESSO</td>
<td>0.79</td>
<td>(0.70, 0.88)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVW(without cofounders)</td>
<td>0.81</td>
<td>(0.72, 0.91)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td>IVW</td>
<td>1.46</td>
<td>(0.96, 2.22)</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>2.04</td>
<td>(1.10, 3.81)</td>
<td>0.028</td>
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</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>0.63</td>
<td>(0.03, 14.4)</td>
<td>0.780</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR-PRESSO</td>
<td>1.46</td>
<td>(0.87, 2.44)</td>
<td>0.168</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVW(without cofounders)</td>
<td>1.62</td>
<td>(0.96, 2.74)</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td>IVW</td>
<td>0.81</td>
<td>(0.60, 1.10)</td>
<td>0.184</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>0.95</td>
<td>(0.61, 1.50)</td>
<td>0.836</td>
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</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>1.00</td>
<td>(0.21, 4.68)</td>
<td>0.998</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR-PRESSO</td>
<td>0.81</td>
<td>(0.61, 1.09)</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVW(without cofounders)</td>
<td>0.53</td>
<td>(0.32, 0.87)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Foot Fracture</td>
<td>IVW</td>
<td>0.78</td>
<td>(0.66, 0.93)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>0.78</td>
<td>(0.61, 0.99)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>0.54</td>
<td>(0.27, 1.05)</td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR-PRESSO</td>
<td>0.78</td>
<td>(0.66, 0.93)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVW(without cofounders)</td>
<td>0.76</td>
<td>(0.62, 0.93)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>IVW</td>
<td>1.39</td>
<td>(0.71, 2.71)</td>
<td>0.330</td>
<td></td>
</tr>
<tr>
<td>Measure</td>
<td>Weighted median</td>
<td>MR Egger</td>
<td>MR-PRESSO</td>
<td>IVW(without cofounders)</td>
<td>IVW</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>------------</td>
<td>-------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td>1.85(0.75,4.59)</td>
<td>0.06(0.00,3.29)</td>
<td>0.39(0.72,2.71)</td>
<td>1.29(0.56,2.98)</td>
<td>1.08(0.79,1.47)</td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td>1.01(0.70,1.46)</td>
<td>2.28(0.46,11.23)</td>
<td>1.08(0.79,1.47)</td>
<td>1.08(0.79,1.47)</td>
<td>0.99(0.59,1.68)</td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>0.83(0.68,1.01)</td>
<td>1.13(0.66,1.93)</td>
<td>0.83(0.73,0.96)</td>
<td>0.81(0.70,0.94)</td>
<td>1.43(0.83,2.49)</td>
</tr>
<tr>
<td>Wrist-hand Fracture</td>
<td>1.88(0.85,4.18)</td>
<td>0.38(0.01,17.88)</td>
<td>1.43(0.76,2.70)</td>
<td>1.55(0.53,4.54)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; MR, mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier.

a. OR are presented for the analyses of binary/dichotomous outcomes.
b. The numbers of SNPs used as IVs in the IVW, weighted median and MR Egger methods and the number of outliers identified and excluded in the MR PRESSO method.

c. $P < 0.05$ was considered significant.

### Table 4. Sensitivity analyses of MR estimates between three phenotypes of socio-economic status and different reflects of osteoporosis and fractures.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Cochran Q test</th>
<th>MR-Egger</th>
<th>MR-PRESSO (global test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q value</td>
<td>P value</td>
<td>Intercept</td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td></td>
<td>56.37</td>
<td>0.035</td>
<td>0.0073</td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>Osteoporosis</td>
<td>352.40</td>
<td>0.0088</td>
<td>-0.0033</td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td></td>
<td>14.42</td>
<td>0.57</td>
<td>-0.033</td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td></td>
<td>132</td>
<td>0.00093</td>
<td>-0.0010</td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>FN-BMD</td>
<td>279</td>
<td>0.065</td>
<td>6.36×10⁻⁵</td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td></td>
<td>15.34</td>
<td>0.50</td>
<td>-0.0081</td>
</tr>
<tr>
<td>Average total household income before tax</td>
<td>eBMD</td>
<td>39</td>
<td>0.00019</td>
<td>-0.0045</td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td></td>
<td>492.26</td>
<td>2.00×10⁻¹²</td>
<td>-0.00029</td>
</tr>
<tr>
<td>Fracture Type</td>
<td>Townsend Deprivation Index at Recruitment</td>
<td>Average Total Household Income before Tax</td>
<td>Townsend Deprivation Index at Recruitment</td>
<td>Average Total Household Income before Tax</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Spine Fracture</td>
<td>303.26</td>
<td>0.31</td>
<td>-0.0034</td>
<td>0.40</td>
</tr>
<tr>
<td>Femur Fracture</td>
<td>313.37</td>
<td>0.19</td>
<td>-0.0021</td>
<td>0.62</td>
</tr>
<tr>
<td>Lower Leg-Ankle Fracture</td>
<td>353.33</td>
<td>0.0081</td>
<td>-0.0020</td>
<td>0.95</td>
</tr>
<tr>
<td>Foot Fracture</td>
<td>347.13</td>
<td>0.015</td>
<td>0.0053</td>
<td>0.26</td>
</tr>
<tr>
<td>Townsend Deprivation Index at Recruitment</td>
<td>31.36</td>
<td>0.012</td>
<td>-0.0020</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Average Total Household Income before Tax**
- Spine Fracture: 44.65
- Femur Fracture: 49.46
- Lower Leg-Ankle Fracture: 59.85
- Foot Fracture: 37.00
<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>SE</th>
<th>BV</th>
<th>SNP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average total household income before tax</td>
<td>64.61</td>
<td>0.011</td>
<td>-0.015</td>
<td>0.35</td>
<td>0.011</td>
</tr>
<tr>
<td>Years of schooling completed</td>
<td>323.24</td>
<td>0.10</td>
<td>-0.0043</td>
<td>0.25</td>
<td>0.10</td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment</td>
<td>19.67</td>
<td>0.18</td>
<td>0.018</td>
<td>0.50</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Abbreviations: FN-BMD, femoral neck bone mineral density; eBMD, bone mineral density from quantitative heel ultrasounds; MR, mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier.

P < 0.05 was considered significant.