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Severe traumatic brain injury and risk for osteoporosis: a Mendelian randomization study

Guoqiang Wang[1], Jiachen Wang[1], Dinglong Yang[1], Lin Liu[1] and Peng Xu[1*]

Abstract

Background The influence of nervous system activity on bone remodeling has been widely reported. Patients with traumatic brain injury (TBI) exhibit a high incidence of osteoporosis (OP). Nevertheless, the relationship between severe TBI (sTBI) and OP remains unclear. We performed Mendelian randomization (MR) analysis to assess the potential causal relationship between sTBI and OP.

Methods Data on exposure and outcomes were acquired from genome-wide association studies (GWAS). Data on OP was obtained from UK Biobank (5,266 cases of OP and 331,893 controls). Data on sTBI was obtained from FinnGen Consortium (6,687 cases and 370,590 controls). Single nucleotide polymorphisms (SNPs) that underwent strict screening were regarded as instrumental variables. We used the inverse variance weighted (IVW), constrained maximum likelihood and model averaging (CML-MA), MR-Egger, and weighted median methods for causal effect estimation. To test the reliability of the results, sensitivity analysis was performed using Cochran's Q, leave-one-out, MR-Egger intercept, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) tests.

Results The IVW analysis indicates that sTBI and OP have a suggestive association (odds ratio [OR] = 1.004, 95% confidence interval [CI] = 1.001,1.007; $p = 0.002$), and no heterogeneity (Q = 11.536, $p = 0.241$) or directional pleiotropy was observed (egger_intercept = 7.368×10^{-5}, $p = 0.870$). The robustness of the results was validated using a leave-one-out sensitivity test.

Conclusion According to the MR analysis, sTBI and OP are likely suggestively related. This finding contributes to the prevention of OP in patients with sTBI and provides genetic evidence supporting the theory that the nervous system regulates bone remodeling.

Keywords Severe traumatic brain injury, Mendelian randomization, Osteoporosis

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Introduction

Osteoporosis (OP) is one of the prevalent chronic metabolic conditions, impacting roughly 200 million individuals globally, including one-third of postmenopausal women and the majority of older adults over the age of 70 [1]. This adds a significant social and economic burden due to its risk of complications such as fractures [2]. It is traditionally believed that OP is caused by the interference of local bone metabolism [3], and the incidence of OP is closely linked to factors such as age, hormone imbalance, diet, and physical exercise [4]. However, recent studies indicate that neuroregulation, one of the three regulatory modes, also plays a significant role in the homeostasis of bone metabolism [5].

As the control center of the human body, the brain controls and regulates the physiological function and dynamic balance of various tissues and organs. After receiving signals from internal organs, such as temperature, electromagnetic signals, and biochemical signals, the brain regulates the internal organs through downlink signals. This process is called interoception [6]. Interoception is an adaptive behavior of the brain that allows it to adjust to changes in the internal and external environment [7]. The central nervous system (CNS) receives signals primarily through sensory nerves distributed throughout various organs and modulates them through descending autonomic nerves (sympathetic and parasympathetic), hormones, and neuropeptides released from the CNS [8]. Bones have abundant sensory and sympathetic innervation [9]. Increasing number of studies consistently affirm that the nervous system tightly regulates bone metabolism [5], indicating that the nervous system is a regulator of OP development. For example, the cAMP-response element binding protein (CREB) signaling pathway in the ventromedial hypothalamic nucleus (VMH) is an important factor affecting bone metabolism via sympathetic nerves [10].

Severe traumatic brain injury (sTBI) refers to an external injury of the head that leads to abnormal brain function, and its Glasgow Coma Scale score is lower than 9 [11]. Approximately 2.53 million people visit emergency departments each year due to TBI-related illnesses [12]. A series of clinical studies indicate that those patients who have suffered TBI can lead to significant bone abnormalities that manifest as an increased risk of osteopenia and OP [13–15]. However, with randomized controlled trials requiring long periods and high economic costs, combined with potential biases such as confounding and reverse causality, the link between sTBI and OP has not been systematically studied. Therefore, this study will use the two-sample Mendelian randomization (MR) method to explore the potential genetic causal relationships between sTBI and OP, and reveal the underlying mechanisms. From a genetic perspective, it will provide insights into the neuroregulatory mechanisms of bone metabolism. Ultimately, this will contribute to the development of more effective prevention and treatment strategies for sTBI patients.

In this study, a two-sample MR design with a high level of evidence was employed to assess the causal associations between exposures and outcomes. This analysis leveraged advancements in database development. By efficiently sidestepping the confounding biases inherent in traditional epidemiological research, this approach uses genetic variation as a tool to deduce a causal link between outcomes and exposure [16].

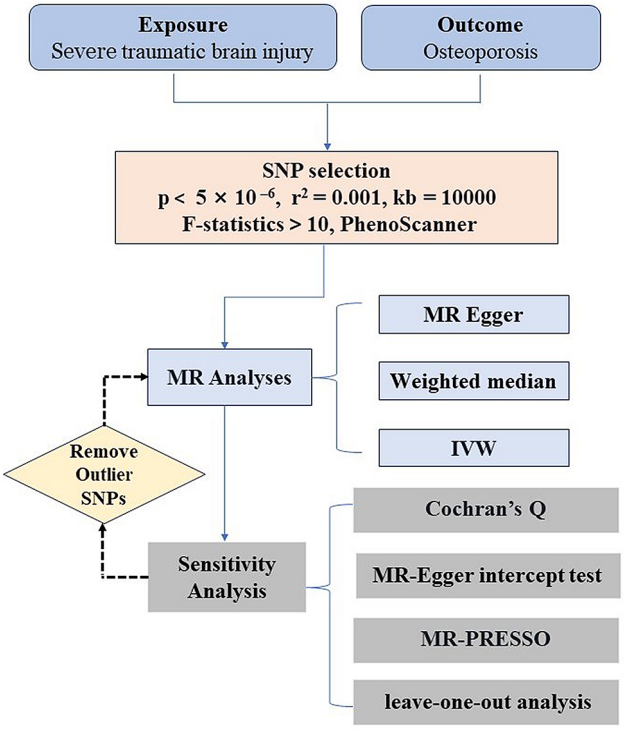

Fig. 1 Study design

Methods

Research overview

Figure 1 is a flow chart detailing the research overview. MR is a powerful approach to determine causation using genetic variation as an instrumental variables (IVs) to evaluate whether a causal relationship exists between exposure and outcome This method effectively prevents confounding bias in conventional epidemiological studies [17]. Gene exposure measurements were obtained from one genome-wide association studies (GWAS) and gene outcome measurements were obtained from another. The MR analysis is grounded in three hypotheses: (I) the IVs are strongly correlated with exposure factors; (II) the IVs and confounding factors are unrelated; and (III) the IVs

are not directly linked to the outcome, with their impact solely reflected through exposure [18].

Data source

sTBI and OP data were sourced from publicly available genome-wide association studies (GWAS) databases, eliminating the need for additional ethical approval.

Summary data for sTBI in the GWAS were sourced from the FinnGen consortium(https://r9.finngen.fi/), which investigates the genomic and national health register data of 500,000 Finnish individuals. Data from the National Health Register for every FinnGen participant were systematically collected and processed. In FinnGen, cases were diagnosed based on hospital records by ICD-10 as S06[2-7], and by ICD-8 and ICD-9 as 85[1-2], comprising 6,687 cases and 370,590 controls. In FinnGen's whole-genome association analysis, adjustments were made for sex, age, the first 10 principal components, and genotyping batches. More detailed information can be found in the published study [19].

Single nucleotide polymorphisms (SNPs) associated with OP were obtained from the Integrative Epidemiology Unit (IEU) OpenGWAS project (https://gwas.mrcieu.ac.uk/, GWAS ID: ukb-a-87). OP phenotype self-reported non-cancer disease codes. A dataset comprising 337,159 individuals of European descent (5,266 cases and 331,893 controls) with 10,894,596 SNPs was generated by the Neale Lab Consortium.

SNP selection

Candidate SNPs closely related to sTBI ($p < 5 \times 10^{-8}$) with only two SNPs and a more liberal p-value were selected because a minimum of 10 IVs were required for MR studies ($p < 5 \times 10^{-6}$) [20], while ensuring that they were not directly linked to the outcome($p > 5 \times 10^{-8}$). In addition, SNPs were clumped to avoid linkage disequilibrium ($r^2 < 0.001$, physical distance = 10000 kb). Strong associations between exposure and SNPs were determined by calculating F-statistics ($F = R^2 \times (N-2)/(1-R^2)$, where N is the sample size and R^2 is the genetic variation. The equation used to calculate R^2 is as follows: $R^2 = 2 \times EAF \times (1-EAF) \times Beta^2$, where EAF represents the effect allele frequency, Beta is the allele effect value, and >10 indicates a strong correlation [21]. Confounding factors were selected using PhenoScanner(http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner). Information on the final IVs used for further MR analyses is shown in the Supplementary Table 1.

MR analyses

Statistical analyses were performed using the two-sample MR package (version 0.5.7) in the R software (version 4.3.1; https://www.r-project.org/).

In the primary analysis, we employed the inverse variance-weighted (IVW) method to investigate the causal relationship between sTBI and OP [22]. In addition to the IVW estimation, we incorporate the MR-Egger and weighted median methods as supplements. These methods offer a more robust estimation across a broader range of scenarios, albeit with a lower efficiency indicated by a wider confidence interval (CI) [23]. Specifically, the weighted median can be used to address some IVW flaws and provide consistent estimates of causal effects, even if 50% of instrumental factors are unreliable [24]. Finally, the use of constrained maximum likelihood and model averaging (CML-MA) methods demonstrated robustness to null IVs with both irrelevant and relevant pleiotropic effects. Therefore, CML-MA can better control the type-I error rate in the estimation [25].

Directional pleiotropy was detected using the intercept of MR-Egger regression [26]. Cochran's Q test was used to evaluate heterogeneity. Additionally, to check whether the observed causal connection was dependent on any specific SNP, we performed a leave-one-out analysis. Finally, an MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test was performed to identify any aberrant values that might have potential pleiotropy [27]. If outliers were discovered, they were deleted and the MR analysis was repeated.

Results

After rigorous screening, 11 sTBI-related SNPs were regarded as IVs for further MR analysis. The lowest F-value of these SNPs was 1098.291, indicating that weak instrumental variables did not influence the accuracy of the results. The IVW analysis revealed a suggestive association between sTBI and OP, with an odds ratio (OR) of 1.004 (95% confidence interval [CI] = 1.001, 1.006; $p = 0.004$). It was also observed in CML-MA (OR = 1.004, 95%CI = 1.001, 1.006; $P = 0.005$). Other MR method analyses (weighted median (OR = 1.003, 95% CI = 0.999,1.006; $P = 0.054$) and MR-Egger (OR = 1.004, 95% CI = 0.997,1.010; $P = 0.299$; Fig. 2) indicated a consistent but insignificant direction. In addition, heterogeneity was not observed in Cochran's Q test (Q = 13.289, $p = 0.208$). More importantly, no directional pleiotropy effect was found in the MR-Egger regression (intercept = -1.456×10^{-5}, $p = 0.974$). The MR-PRESSO test revealed no abnormalities between the sTBI and OP risk (Supplementary Table 2). In the leave-one-out analysis, the results indicated that no individual SNP exhibited strong inconsistencies with the overall effect of sTBI on OP (Fig. 3A).

We searched the human genotype-phenotype association database Phenoscanner V2 to determine whether these SNPs were correlated with potential risk factors. These factors include smoking, being overweight, body

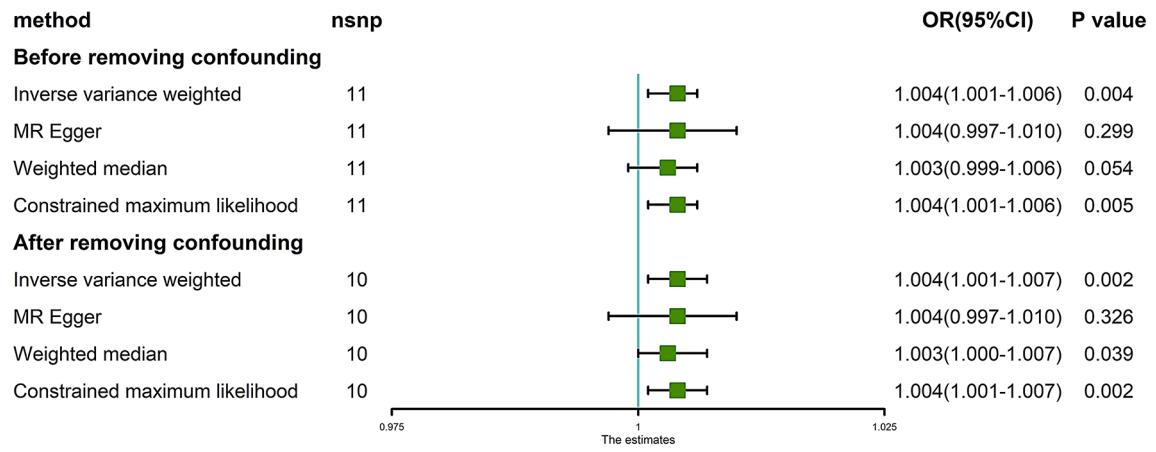

Fig. 2 Mendelian randomization results of causal effects between sTBI and OP

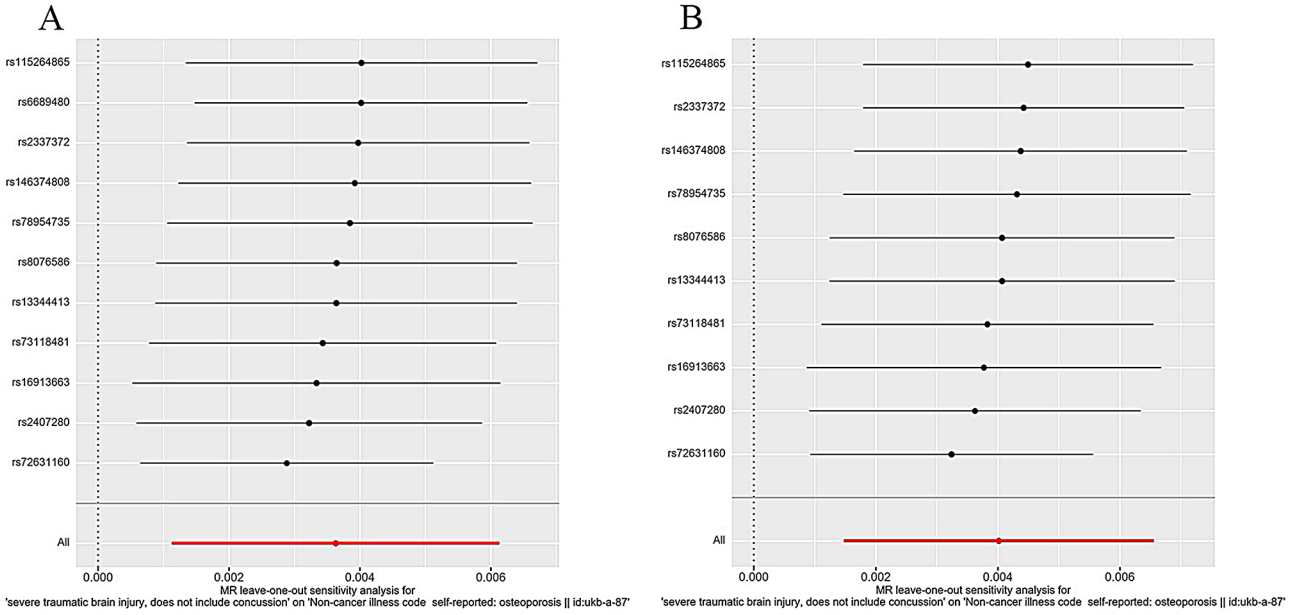

Fig. 3 Leave-one-out analysis for sTBI on OP. **A**: Analysis results before removing confounding factors. **B**: Analysis results after removing confounding factors

mass index (BMI), bone disease, thyroid disease, diabetes, rheumatoid arthritis, and ankylosing spondylitis [28]. After screening, rs6689480 (2.42×10^{-6}) associated with BMI was deleted. At last, 10 SNPs was used for the final MR analysis, IVW (OR = 1.004, 95% CI = 1.001, 1.007; $p = 0.002$), CML-MA (OR = 1.004, 95% CI = 1.001, 1.007; $p = 0.002$) and Weighted median (OR = 1.003,95% CI = 1.000, 1.007; $p = 0.039$; Fig. 4) indicated that there was a suggestive association between sTBI and OP.MR-Egger analysis revealed a contributory but not statistically significant effect of sTBI on the risk of OP (OR = 1.004, 95% CI = 0.997,1.010], $p = 0.326$; Fig. 2). The MR-Egger intercept P value showed no pleiotropy ($P = 0.870$) or Cochran's Q test statistic, and its P value showed no heterogeneity (Q = 11.536, $P = 0.241$; Supplementary Table 2). The robustness of the results was validated using a leave-one-out sensitivity test (Fig. 3 B).

Discussion

The present study used a large sample size of GWAS data to reveal the potential causal relationship between sTBI and OP using a two-sample MR. An OR of 1.004 indicated a suggestive association between the genetic risk of OP and sTBI. Previous observational studies revealed a significant association between TBI and OP. The results of a cross-sectional study of 112 patients with acquired brain injury (ABI) showed that 21.4% of patients had OP, 41.1% had osteopenia, and 27.7% are vitamin D deficient [13]. In another study, 18% of TBI patients undergoing neurobehavioral rehabilitation had radial osteopenia,

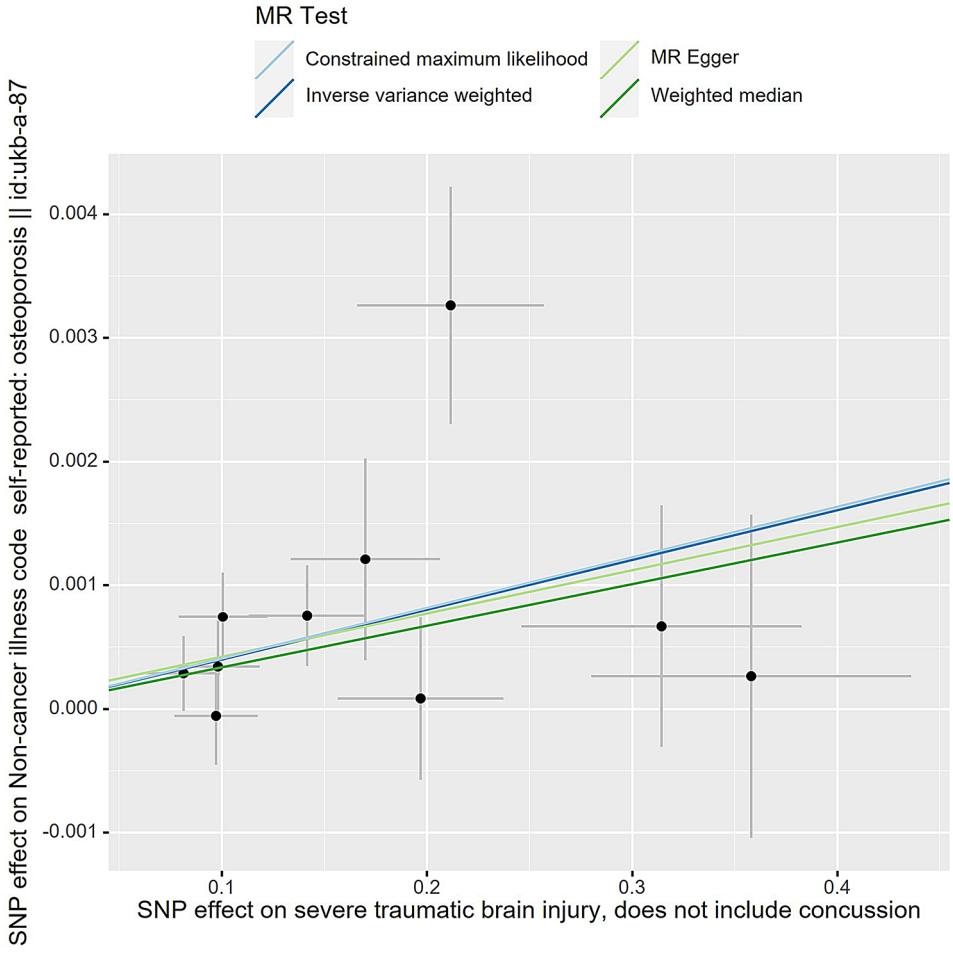

Fig. 4 Scatter plot of MR analyses for the associations of sTBI with risk of OP

and 51% had OP or osteopenia in the tibia [29]. Based on these findings, TBI may be a risk factor for OP development.

Previously, it was generally believed that OP was caused by the disruption of the dynamic balance of local osteogenesis and osteoclast processes due to genetics, exercise, hormones, and other factors. However, as one of the three major regulatory modes in the human body, neuromodulation has not attracted much attention. Traditionally, we hypothesized that TBI causes OP largely due to physical inactivity; however, in the TBI rat model, TBI led to bone loss distant from the injury site, regardless of activity [30]. Therefore, a deeper understanding of this mechanism is required.

In recent years, Professor Cao Xu has proposed an important role for neural regulation in musculoskeletal diseases, which is called skeletal interoception. The proposal and demonstration of this concept breaks the traditional thinking framework and promotes research in the field of nervous system regulation in bones [5]. According to research in the field of skeletal interoception, as there are a large number of sensory and autonomic nerves distributed on the bones, the CNS, as the control center of the human body, receives a variety of signals transmitted by skeletal sensory nerves, such as mechanical, temperature, and biochemical signals. After integrating and processing these signals, it releases regulatory signals to the bones through autonomic nerves and participates in the regulation of bone status, thereby playing a role in the development of bone diseases such as OP, osteoarthritis (OA), lumbar degenerative disease, and so on [5]. Cao et al. found that prostaglandin E2 (PGE2) secreted by osteoblasts on the bone surface acts on the prostaglandin E (EP) receptor 4 (EP4) of sensory nerves, which activates the CREB signaling pathway of the VMH. This inhibits activation of the descending sympathetic nerve, which promotes osteogenic differentiation, inhibits adipogenic differentiation of bone marrow mesenchymal stromal cells (bMSCs) and mediates osteogenesis [10, 31]. Similarly, bone PGE2-mediated ascending interoceptic signals induce small heterodimer partner-interacting leucine zipper protein (SMILE) expression in the hypothalamus. SMILE acts as a transcriptional heterodimer on the neuropeptide Y (NPY) promoter and

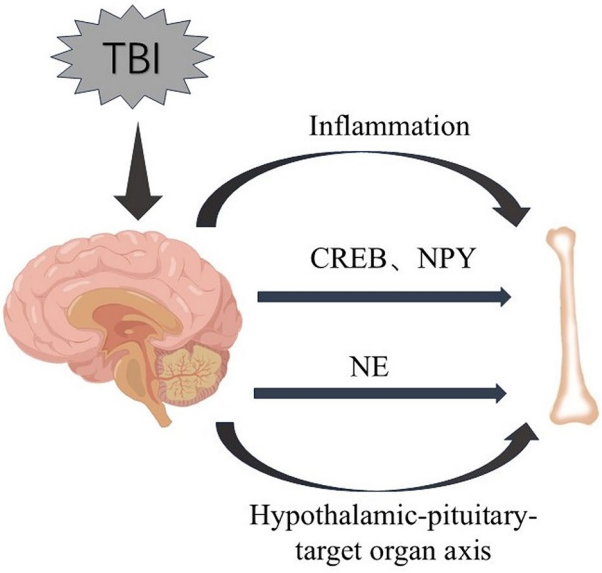

Fig. 5 The central nervous system (CNS) plays an important role in bone metabolism. Traumatic brain injury (TBI) impairs the normal function of the brain, resulting in an increased risk of osteopenia and osteoporosis. CREB: cAMP-response element binding protein; NPY: neuropeptide Y; NE: norepinephrine

binds to phosphorylated CREB to inhibit NPY expression. Downregulation of hypothalamic NPY expression directs free fatty acids towards anabolic bone formation through neuroendocrine downdescending interoceptive regulation [32]. Indeed, these studies have revealed an important role of the CNS in the regulation of bone homeostasis. However, TBI inevitably damages the normal structure and function of the brain, which affects the normal metabolic regulation of the CNS in the peripheral bones. The study of intraosseous sensations provides a new explanation and research direction for OP caused by TBI (Fig. 5).

In recent experimental studies, norepinephrine (NE) levels in the serum of patients with TBI were significantly increased at 7 and 14 days after TBI, and the levels of NE in the bone marrow supernatant were significantly increased in the TBI group [33]. In TBI-treated mice, the expression of tyrosine hydroxylase (TH) in the hypothalamic paraventricular nucleus (PVN), a key area of sympathetic outflow, was significantly increased. Other studies have shown that microgravity may lead to bone loss through sympathetic overactivity during space flight [34]. Therefore, the promoting effect of TBI on sympathetic nerve function is one of the reasons for the observed decrease in bone mass. The hypothalamus-pituitary-target organ axis is an important part of neuroendocrine regulation that precisely regulates the homeostasis of energy metabolism in the bone and other organs [5]. Hypothalamic-pituitary dysfunction is present in 70% of patients with brain injury [35]. After Three months after brain injury, 56% of patients had at least one pituitary axis impairment, and after 12 months, 36% still had defects [36]. Long-term lack of growth hormone (GH) and thyroid-stimulating hormone (TSH) in patients with TBI significantly affects bone metabolism due to hypopituitarism. GH deficiency promotes bone fragility and decreases bone mass [37]. Reduced TSH levels significantly enhanced bone resorption and diminished bone osteogenesis [38]. This evidence indicates that TBI can lead to the destruction of the hypothalamic-pituitary function, thus affecting bone metabolism and promoting OP. The above studies are consistent with those on bone sensation, and the mechanism by which TBI leads to OP has been preliminarily explored.

Local and systemic inflammatory responses caused by TBI are also possible causes of bone loss. CNS injury causes metabolic disorders, apoptosis, oxidative stress and neuroinflammation [39, 40]. At the same time, TBI causes the mechanical shear force and tear force generated by the movement of the brain in the skull to lead to the release of neuropeptides, increase the permeability of the blood-brain barrier, and enhance the inflammatory response, which further produces a positive feedback with neurogenic inflammation [41], triggering a systemic immune inflammatory response, in which complex inflammatory cells and molecular cascades, such as interleukin 6 (IL-6), IL-11 and nuclear factor kappa B (NF-κB) signaling pathways, promote bone catabolism [42, 43].

However, few studies have conclusively demonstrated the biological basis for this link, because these results are either based on small samples or simply examine the correlation from epidemiological observations. Through the application of the MR method, the limitations of observational research can be effectively avoided by using the MR-Egger regression to detect directional pleiotropy, and using Cochran's Q test to evaluate the variables can reveal our results more confidently. Generally, the IVW method is significantly more effective than the other MR methods, particularly the MR-Egger [44]. Therefore, it is not surprising that the MR-Egger results in this investigation, with low statistical efficacy, showed larger confidence and non-indigenous P-values when compared to IVW. The robustness of the IVW estimation was confirmed through sensitivity and pleiotropy analyses.

The unique strength of this study lies in the integration of genetic insights to explore the role of neuroregulatory mechanisms in bone metabolism. Previous studies have generally attributed the development of OP following sTBI to a lack of physical activity. It was believed that insufficient exercise directly led to a decrease in bone density, thus triggering the onset of OP. However, our research offers a new perspective, emphasizing the potential role of neuroregulatory processes in the development of OP following sTBI. Specifically, after

excluding confounding factors such as physical activity, the neurophysiological changes induced by sTBI may impact the neuro-bone interaction, alter the secretion of bone metabolism-related hormones, or modify the neuroregulation of bones, thus leading to the development of OP. This finding suggests that neuroregulatory factors may play a significant role in the onset of OP after sTBI, providing a new perspective for the clinical development of more comprehensive treatment and prevention strategies. It highlights the need to not only focus on changes in physical activity but also consider the role of neuroregulatory mechanisms in bone health.

It has been reported that the physical manifestations of abnormal bone metabolism after TBI may only be detected after severe bone injuries occur [15]. Given that sTBI is a clear risk factor for OP, we recommend incorporating bone health management into the care of sTBI patients. After experiencing sTBI, especially during the rehabilitation phase, patients may not yet show obvious symptoms of abnormal bone metabolism. Doctors can use bone density testing or biomarker monitoring to detect potential OP risks early, allowing them to develop personalized bone health management plans that combine medication interventions and lifestyle adjustments to improve the patient's bone metabolism comprehensively. From a public health perspective, early screening and preventive interventions should be promoted, especially among the sTBI patient population. A standardized process for screening and managing post-TBI osteoporosis should be established. By increasing health education, raising awareness of the risks of post-TBI osteoporosis, and providing relevant treatment options, patients can be helped to identify issues early and take proactive interventions.

However, this study has some limitations. First, when selecting SNPs, when $p < 5 \times 10^{-8}$, there are only two SNPs did not meet the minimum requirements for MR analysis. Therefore, we relaxed the significance threshold (5×10^{-6}) in the SNP selection process. This method has been used in previous studies [20, 45]. However, this would lead to a weaker correlation between some SNPs and traits; therefore, we calculated the F-statistic to evaluate this bias. Although no IVs with F less than 10 were found, we still recommend caution should be exercised when interpreting these results. Second, all GWAS data originated from European populations, which may limit the generalizability of the results to other racial groups. Since allele frequencies and effect sizes of genetic variants may differ in non-European populations, causal estimates in MR analyses could be affected. Third, it is difficult to determine the biological function of these SNPs, so the horizontal pleiotropy effect cannot be completely avoided. Finally, uncertainty exists regarding the metabolic mechanisms underlying the association between sTBI and OP remain unclear. Due to these limitations, future studies are essential to confirm this relationship, explore potential mechanisms, and we emphasize the need for future research to include more diverse genetic datasets to validate the applicability of these relationships across different racial groups.

Conclusion

Our results suggest an association between sTBI and OP. Considering the high incidence of TBI and OP in the general population, large-scale prospective and mechanistic studies are crucial to provide a clearer illustration of the relationship between sTBI and OP.

Abbreviations

sTBI	Severe traumatic brain injury
OP	Osteoporosis
MR	Mendelian randomization
GWAS	Genome-wide association study
SNPs	Single nucleotide polymorphisms
IVW	Inverse variance weighted
MR-PRESSO	MR Pleiotropy RESidual Sum and Outlier
CML-MA	Constrained maximum likelihood and model averaging
CNS	Central nervous system
CREB	CAMP-response element binding protein
VMH	Ventromedial hypothalamic nucleus
IVs	Instrumental variables
IEU	Integrative Epidemiology Unit
BMI	Body mass index
PGE2	Prostaglandin E2
EP4	Prostaglandin E (EP) receptor 4
bMSCs	Bone marrow mesenchymal stromal cells
SMILE	Small heterodimer partner-interacting leucine zipper protein
NPY	Neuropeptide Y
NF-κB	Nuclear factor kappa B
IL	Interleukin
TH	Tyrosine hydroxylase
GH	Growth hormone
TSH	Thyroid-stimulating hormone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-025-02127-2.

Supplementary Material 1

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Author contributions

Peng Xu and Guoqiang Wang designed the study. Guoqiang Wang and Jiachen Wang, analyzed the datasets and interpreted the results. Software support was provided by Dinglong Yang and Lin Liu. Guoqiang Wang and Jiachen Wang wrote and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

The data are available from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) and FinnGen consortium (https://r9.finngen.fi/), which was used in this study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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