Genetic Associations Between Common Medication Use and Osteoporosis-Related Outcomes: A Mendelian Randomization Study

Keywords
Osteoporosis, Drug-Related Side Effects and Adverse Reactions, Mendelian Randomization Analysis, Thyroid Hormones, Anilides, Antidiabetic Agents

Abstract

Introduction
Osteoporosis pathogenesis involves a complex interplay of genetic predisposition and medication exposure. Although long-term medication use contributes to bone fragility, which is distinct from osteomalacia, genetic evidence linking common medication-use traits to osteoporosis remains limited.

Material and methods
Two-sample Mendelian randomization (MR) analyses utilized GWAS data for 22 medication-use traits (UK Biobank) and osteoporosis outcomes (FinnGen R12). Multivariable MR (MVMR) was employed to adjust for confounding by underlying disease indications. Primary estimates were derived using the inverse variance–weighted (IVW) method, supported by comprehensive sensitivity analyses including MR-Egger, weighted median, and MR-PRESSO to evaluate heterogeneity and pleiotropy.

Results
Univariable MR identified seven significant associations: anilide use with increased osteoporosis risk (OR=1.25, FDR=0.0201); immunosuppressant use with higher risks of osteoporosis with pathological fracture (OR=1.16, FDR=0.0074) and drug-induced osteoporosis (OR=1.36, FDR=0.0168); thyroid preparations with increased osteoporosis (OR=1.08, FDR=0.0016), drug-induced osteoporosis, and osteoporosis with pathological fracture; and an inverse association between antidiabetic drug use and osteoporosis (OR=0.88, FDR=0.0002). In MVMR, associations for anilide and thyroid preparation use remained significant after adjusting for back pain and hypothyroidism, respectively. However, the antidiabetic signal reversed after type 2 diabetes adjustment, indicating the observed benefit was likely confounded by the underlying metabolic condition rather than a direct pharmacological effect.

Conclusions
Genetic evidence supports that anilide and thyroid hormone use may independently increase osteoporosis risk, while the protection from antidiabetic therapy is confounded by diabetes status. Medication-related osteoporosis should be considered in long-term pharmacologic management.

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Abstract

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Methods: Two-sample Mendelian randomization (MR) analyses utilized GWAS data for 22 medication-use traits (UK Biobank) and osteoporosis outcomes (FinnGen R12). Multivariable MR (MVMR) was employed to adjust for confounding by underlying disease indications. Primary estimates were derived using the inverse variance‐weighted (IVW) method, supported by comprehensive sensitivity analyses including MR-Egger, weighted median, and MR-PRESSO to evaluate heterogeneity and pleiotropy.

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Conclusion: Genetic evidence supports that anilide and thyroid hormone use may independently increase osteoporosis risk, while the protection from antidiabetic therapy is confounded by

diabetes status. Medication-related osteoporosis should be considered in long-term pharmacologic management.

Key words: Mendelian Randomization Analysis, Osteoporosis, Drug-Related Side Effects and Adverse Reactions, Anilides, Thyroid Hormones, Antidiabetic Agents, Genetic Association, Pharmacology, Management

Highlights:

- Anilide and thyroid hormone use are genetically associated with increased osteoporosis risk.
- Antidiabetic drug use shows a protective association only before adjusting for type 2 diabetes.
- Immunosuppressant-related osteoporosis risk is largely driven by underlying rheumatoid arthritis.
- Medication-related bone fragility warrants regular monitoring in long-term users.

Introduction

Osteoporosis is a chronic metabolic bone disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased fragility and fracture risk[1]. Its clinical manifestations primarily include pathological and fragility fractures at typical sites such as the femur, lumbar spine, and pelvis[2]. Epidemiologically, vertebral fractures are among the most common, with an imaging-based prevalence of approximately 30% in women and 19% in men over age 50, typically assessed via morphometry on lateral spine imaging [2]. Globally, osteoporosis affected approximately 41.5 million individuals in 2019 and is projected to rise to 263 million by 2034, representing a major and growing public health burden, particularly among individuals aged ≥50 years[3]. Although age, hormonal imbalance, and metabolic dysregulation are established contributors, emerging evidence highlights the role of long-term medication exposure in accelerating bone loss and fracture susceptibility[4]. Given the widespread and often chronic use of medications in older adults, elucidating their potential associations with osteoporosis risk is critical for improving risk stratification and precision prevention [5].

A number of commonly used medications have been implicated in adversely affecting bone health [6]. For instance, long-term glucocorticoid therapy is the most frequent cause of iatrogenic osteoporosis, with fractures occurring in up to 30–50% of patients under chronic use[7, 8]. It induces rapid bone loss, especially within the first months of treatment, through pathways including suppression of osteoblast activity, promotion of osteoclastogenesis, and reduced intestinal calcium absorption [7]. Thyroid hormone therapy (e.g. levothyroxine) has been associated with reduced bone mass and altered bone metabolism, primarily by stimulating osteoclast activity and accelerating the bone remodeling process [9]. Although these associations have been frequently observed in epidemiological studies, they are often influenced by

confounding from underlying diseases and clinical treatment indications [10]. Mendelian randomization (MR) uses genetic variants as instrumental variables (IVs) to estimate potential causal effects while minimizing bias from environmental and clinical factors, providing a reliable approach to disentangle complex relationships[11]. Previous MR studies have reported heterogeneous effects of antidiabetic, lipid-lowering, thyroid-related, and reproductive factors on osteoporosis risk or bone mineral density (BMD)[12-15]. However, these studies have focused on single drug classes and outcomes [16]. This limitation necessitates a comprehensive genetic assessment spanning multiple medication-use and skeletal phenotypes, encompassing osteoporosis, pathological fractures, and other related skeletal outcomes, to clarify medication-related associations and guide safer strategies for osteoporosis prevention and management [10], such as providing a genetic basis for personalized medication decisions and reinforcing bone health monitoring in long-term users of implicated drugs.

Therefore, to overcome the limitations of previous piecemeal analyses, we conducted a comprehensive, systematic genetic investigation. This study aimed to simultaneously evaluate the genetic associations of a broad spectrum of common medication classes with multiple osteoporosis-related skeletal outcomes, and to employ multivariable MR (MVMR) to disentangle direct pharmacologic effects from confounding by underlying disease indications. By integrating this dual analytical framework across diverse drug categories and phenotypes, our work provides novel, genetically-informed evidence on medication-related osteoporosis risk, with the ultimate goal of guiding safer prescribing practices and targeted bone health monitoring.

Materials and methods

Study design

This study followed a pre-defined, stepwise analytical plan to assess the causal role of medication use in osteoporosis. The methodology adhered to the STROBE-MR reporting guidelines [17], and the overall analytical workflow is conceptually outlined in **Figure 1**. The detailed sequence of steps is as follows:

Step 1. Data Acquisition and Instrumental Variable (IV) Selection. We obtained summary-level genetic data from large-scale genome-wide association studies (GWAS). This included: (i) 22 medication-use traits as exposures (UK Biobank), (ii) osteoporosis and related fracture outcomes (FinnGen R12), and (iii) genetic predispositions to key confounding diseases (e.g., type 2 diabetes, back pain; Million Veteran Program). For each trait, independent single-nucleotide polymorphisms (SNPs) meeting genome-wide significance ($P < 5\times10^{-8}$) and linkage disequilibrium ($R^2 < 0.001$) criteria were selected as IVs, ensuring adherence to the three core MR assumptions [18].

Step 2. Univariable Mendelian Randomization Analysis. Using the selected IVs, we first performed two-sample MR analyses for each exposure-outcome pair to estimate the total genetic association. The primary causal estimate was derived using the inverse-variance weighted (IVW) method, with sensitivity estimates from MR-Egger, weighted median, and weighted mode methods.

Step 3. Multivariable MR for Confounding Adjustment. To disentangle the direct effect of medication use from the effect of the underlying disease indication, we performed multivariable MR (MVMR). For each significant or candidate medication, such as anilides, thyroid drugs, we included the genetic instruments for both the medication and its corresponding indication disease such as back pain, hypothyroidism in a joint model using the multivariable IVW method.

Step 4. Sensitivity and Robustness Validation. The validity of all significant associations from Steps 2 and 3 was rigorously tested. This involved: (i) assessing heterogeneity among IVs using Cochran's Q statistic; (ii) testing for horizontal pleiotropy using MR-Egger intercept and MR-

PRESSO global tests; and (iii) conducting leave-one-out analyses to ensure results were not driven by a single influential SNP.

Data sources

GWAS data for drug exposure traits were obtained from a large-scale UK Biobank analysis by Wu et al., who performed GWAS of 23 self-reported medication-use categories in approximately 320,000 participants of European ancestry to identify genetic variants associated with medication-taking behaviors[19]. After excluding drugs affecting bone structure and mineralization use measurement (GCST007935) because of its direct biological relevance to osteoporosis outcomes, 22 medication-use traits were retained for analysis.

Outcome data for osteoporosis and related phenotypes were derived from the FinnGen R12 cohort, including osteoporosis (M13_OSTEOPOROSIS; 10,461 cases and 473,264 controls), osteoporosis with pathological fracture (OSTEOPOROSIS_FRACTURE_FG; 2,429 cases and 374,317 controls), fracture of the femur (ST19_FRACT_FEMUR; 12,229 cases and 476,877 controls), fracture of the lumbar spine and pelvis (ST19_FRACT_LUMBAR_SPINE_PELVIS; 9,061 cases and 481,639 controls), coxarthrosis (M13_ARTHTROSIS_COX; 30,802 cases and 315,115 controls), and drug-induced osteoporosis (DRUGADVERS_OSTEOPO; 389 cases and 499,959 controls). Diagnostic definitions for the outcomes were based on national registry data using standardized ICD-8, ICD-9, and ICD-10 codes.

To account for potential confounding from underlying diseases, MVMR was performed using GWAS summary data from the Million Veteran Program (MVP). The included traits were type 2 diabetes (T2D; Phe_250_2; 154,194 cases and 278,454 controls), hypothyroidism (Phe_244; 62,814 cases and 378,321 controls), rheumatoid arthritis (RA; Phe_714_1; 10,479 cases and

436,161 controls), and back pain (Phe_760; 218,071 cases and 185,068 controls), corresponding respectively to antidiabetic, thyroid, immunosuppressant, and anilide exposures.

All included traits are summarized in **Table 1**. This study used only publicly available, de-identified GWAS summary statistics. All original studies received ethical approval from their respective institutional review boards, and informed consent was obtained from participants. No additional ethical approval or consent was required for the present analyses. The original data used in this study, including the summary statistics and the full code used for the MR and MVMR analyses, have been uploaded to the Zenodo database with the DOI: [https://doi.org/10.5281/zenodo.17970613]. The data can be accessed via the following link: [https://doi.org/10.5281/zenodo.17970613].

Selection of IVs

SNPs associated with each exposure were selected at a genome-wide significance threshold of $P < 5 \times 10^{-8}$. For exposures yielding fewer than four instruments, a relaxed threshold of $P < 5 \times 10^{-6}$ was applied[20], including peptic ulcer and GORD drugs (GCST007922), vasodilators used in cardiac diseases (GCST007925), antihypertensives (GCST007926), immunosuppressants (GCST007933), opioids (GCST007936), anilides (GCST007938), and antidepressants (GCST007940). SNPs with a minor allele frequency (MAF) ≤ 0.01 were excluded to avoid bias from rare variants. Linkage disequilibrium (LD) pruning was conducted using an $R^2 < 0.001$ and a window size of 10,000 kb to retain independent variants. When a selected SNP was unavailable in the outcome dataset, a proxy SNP in high LD ($R^2 > 0.8$) was substituted. The strength of each IV was evaluated using the F statistic, calculated as $F = R^2 \times (N - 2) / (1 - R^2)$. R^2 represents the proportion of exposure variance explained by the SNP. Instruments with F values ≤ 10 were excluded to minimize weak instrument bias[21].

Outlier removal

The MR-PRESSO framework was applied for outlier detection and correction, including a global test for overall pleiotropy, an outlier test to identify and remove heterogeneous variants, and a distortion test to assess whether causal estimates changed significantly after correction[22]. Additionally, an LOO analysis was conducted for each exposure–outcome pair to evaluate the influence of individual SNPs on the overall MR estimate. For exposure–outcome pairs that still exhibited heterogeneity or horizontal pleiotropy, the LOO procedure was further performed iteratively by excluding the most influential variant in each round, repeating the MR-PRESSO, MR-Egger heterogeneity (Q-test), and MR-Egger intercept tests until all three criteria were simultaneously satisfied (MR-PRESSO global test $P > 0.05$, MR-Egger Q-test $P > 0.05$, and MR-Egger intercept $P > 0.05$).

Univariable MR analysis

Putative causal effects between each medication-use trait and osteoporosis-related outcomes were estimated using four complementary MR models: inverse variance–weighted (IVW), MR-Egger, weighted median, and weighted mode. The IVW method served as the primary analysis to provide pooled causal estimates under the assumption of no horizontal pleiotropy. The remaining three approaches were applied to assess the stability and consistency of the results[23]. Multiple testing correction was applied to IVW-derived P values using the Benjamini–Hochberg method. A false discovery rate (FDR) < 0.05 was considered statistically significant.

Sensitivity analysis

To assess the validity of IVs and the robustness of causal estimates, a series of sensitivity analyses was performed. Heterogeneity among SNPs was evaluated using Cochran's Q statistic under the IVW model ($P < 0.05$ indicating significant heterogeneity). Horizontal pleiotropy was examined

using the MR-Egger intercept test ($P < 0.05$ suggesting directional pleiotropy) and further assessed through the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test [24, 25].

MVMR

To control for confounding by underlying disease indications, multivariable MR was performed using genome-wide significant SNPs ($P < 5 \times 10^{-8}$, MAF > 0.01) associated with both drug-use exposures and corresponding disease traits [26]. LD pruning was independently conducted for each trait using $R^2 < 0.001$ and a 10,000 kb window to remove correlated variants. The pruned SNP sets from all exposures and confounders were merged, deduplicated, and re-pruned under the same parameters to generate a pool of mutually independent candidate variants. From this joint set, SNPs were extracted separately for the exposure and confounder datasets. To ensure strand consistency, exposure datasets were treated as exposures and confounder datasets as outcomes during harmonization. Effect alleles were corrected for non-palindromic variants, and all palindromic SNPs were excluded. After harmonization, only SNPs present in both exposure and confounder datasets were retained as final IVs. MVMR analyses were conducted using the multivariable IVW approach to estimate the effects of each exposure while accounting for correlated traits [27].

Statistical analysis and image generation

All statistical analyses were conducted using R software (version 4.3.0) with the "TwoSampleMR" package. Scatter, Forest, and funnel plots were generated to visualize MR results.

Results

IV selection

Osteoporosis is often clinically silent until a fracture occurs. Its most common manifestations are fragility fractures resulting from minimal trauma, typically at the spine, hip, or wrist. Vertebral fractures can lead to back pain, height loss, and kyphosis, while hip fractures are associated with significant morbidity and mortality; large-scale studies have recorded tens of thousands of deaths attributable to such fractures [28]. The outcomes analyzed in this study directly capture these critical clinical endpoints. In postmenopausal women, the accelerated bone loss that primarily underlies osteoporosis is driven by estrogen deficiency. This hormonal change leads to increased bone resorption, resulting in rapid reduction of bone mineral density and deterioration of trabecular microstructure [29], thereby increasing skeletal fragility. Our analysis of osteoporosis-related genetic associations directly addresses this significant clinical and public health burden.

After harmonization and quality control, independent genome-wide significant variants were selected for 22 medication-related exposures. Outlier detection and sensitivity analyses were performed for all exposure–outcome pairs. To ensure robust causal estimates, SNPs with significant horizontal pleiotropy or undue influence were excluded through a two-step procedure: (1) initial outlier detection using the MR-PRESSO framework, followed by (2) an iterative leave-one-out (LOO) analysis for pairs where heterogeneity persisted. The LOO iteration continued until the estimates satisfied pre-specified criteria for heterogeneity and pleiotropy (all $P > 0.05$). The list of excluded SNPs is detailed in **Table S1**. After exclusion, all retained IVs satisfied the predefined convergence criteria. The final number of SNPs per exposure–outcome pair ranged from 4 (antihistamine–coxarthrosis) to 142 (renin–angiotensin system agents–drug-induced osteoporosis).

MR analyses of medication use and osteoporosis-related skeletal outcomes

Using the IVW method, significant associations (FDR < 0.05) were observed for anilide use with elevated osteoporosis risk (OR = 1.25, 95% CI: 1.09–1.44, FDR = 0.0201); immunosuppressant

use with higher risks of osteoporosis with pathological fracture (OR = 1.16, 95% CI: 1.07–1.26, FDR = 0.0074) and drug-induced osteoporosis (OR = 1.36, 95% CI: 1.13–1.64, FDR = 0.0168); thyroid preparations with increased risks of osteoporosis (OR = 1.08, 95% CI: 1.04–1.12, FDR = 0.0016), drug-induced osteoporosis (OR = 1.37, 95% CI: 1.17–1.61, FDR = 0.0021), and osteoporosis with pathological fracture (OR = 1.12, 95% CI: 1.05–1.19, FDR = 0.0158). Conversely, antidiabetic drug use was inversely associated with osteoporosis (OR = 0.88, 95% CI: 0.84–0.93, FDR = 0.0002). Several additional IVW associations reached nominal significance ($P < 0.05$ but FDR ≥ 0.05), including anilides, glucocorticoids, HMG-CoA reductase inhibitors, immunosuppressants, and inhalant adrenergics with osteoporosis and related skeletal disorders **(Table 2)**. Results from supplementary MR methods (MR-Egger, weighted median, and weighted mode) were largely consistent in direction and magnitude with the IVW estimates **(Table S2)**. The scatter **(Figure 2)** and forest plots **(Figure S1)** for FDR-significant associations demonstrated consistent SNP-specific effects and overall MR estimates across methods. The corresponding funnel and LOO plots showed symmetric distributions and the absence of influential single variants **(Figure S2–S3)**.

Sensitivity analyses

Sensitivity analyses were conducted to assess heterogeneity and horizontal pleiotropy for all exposure–outcome pairs after outlier correction. As shown in **Table S3**, Cochran's Q test indicated no significant heterogeneity ($P > 0.05$), and the MR-Egger intercept test showed no evidence of directional pleiotropy ($P > 0.05$). Additionally, the MR-PRESSO global test detected no residual horizontal pleiotropy ($P > 0.05$) in any exposure–outcome combination **(Table S4)**. These findings indicate that the IVs used in the MR analyses were generally valid and that the estimated associations were unlikely to be biased by heterogeneity or unbalanced pleiotropy.

MVMR analysis

MVMR was conducted to determine whether the associations identified in univariable MR persisted after adjusting for underlying disease indications. As shown in **Table 3**, the associations of anilide use with elevated osteoporosis risk (OR = 1.25, 95% CI: 1.06–1.48, P = 0.0084) and thyroid preparation use with increased risks of osteoporosis (OR = 1.14, 95% CI: 1.08–1.21, P = 1.3×10^{-5}) and osteoporosis with pathological fracture (OR = 1.17, 95% CI: 1.05–1.31, P = 0.004) remained significant after controlling for back pain and hypothyroidism, respectively. In contrast, the previously protective association between antidiabetic drug use and osteoporosis in univariable MR reversed after adjustment for T2D (OR = 1.13, 95% CI: 1.03–1.25, P = 0.008), indicating that the benefit was likely driven by disease-related confounding. Similarly, the associations of thyroid preparations and immunosuppressants with drug-induced osteoporosis, and immunosuppressant use with osteoporosis with pathological fracture, lost significance after controlling for hypothyroidism or RA, suggesting that these relationships were largely attributable to the underlying disease indications rather than the medications themselves.

Discussion

In this study, MR and MVMR analyses identified independent associations of anilide use with increased osteoporosis risk and thyroid preparations with higher risks of osteoporosis and osteoporosis with pathological fracture [30, 31]. The inverse association between antidiabetic drug use and osteoporosis in univariable MR was reversed after adjusting for T2D, reflecting confounding by indication [32]. Similarly, associations of thyroid preparations and immunosuppressants with drug-induced osteoporosis lost significance after controlling for hypothyroidism or RA, suggesting disease-related rather than pharmacologic effects [33]. These

findings indicate that prolonged use of anilide-containing analgesics, thyroid hormone replacement, and antidiabetic medications may increase bone fragility, warranting regular bone density monitoring and timely preventive intervention in long-term users.

By integrating univariable and multivariable MR approaches [34], this study revealed medication-related skeletal effects while accounting for confounding by underlying disease indications. The consistent associations of anilide and thyroid hormone use with increased osteoporosis risk, together with the reversal of the antidiabetic drug association and the loss of significance for immunosuppressant use after adjustment, indicate that the applied framework effectively differentiated pharmacologic from disease-related influences. This dual-level analysis enhances the reliability of genetically inferred associations and underscores the methodological value of genetically predicted medication-use traits for evaluating drug safety at the population scale.

Anilides, primarily paracetamol, are among the most commonly used analgesics [19, 35]. While epidemiological studies have associated their regular use with increased fracture risk [36], our Mendelian randomization analysis provides novel genetic evidence supporting a potential causal role of anilide use in osteoporosis, independent of conventional behavioral confounders. The underlying mechanisms may involve the inhibition of bone-forming osteoblast activity through cyclooxygenase suppression, coupled with reduced mobility due to chronic pain[37, 38]. Therefore, our findings reinforce and extend previous observational concerns by suggesting a genetic predisposition to anilide use is linked to bone fragility, warranting heightened vigilance regarding bone health in long-term users.

The observed association between thyroid preparation use and increased osteoporosis risk aligns with extensive evidence that thyroid hormones accelerate bone turnover [39]. It is noteworthy that vitamin D status, a key regulator of calcium homeostasis, interacts with thyroid function and may

modulate the skeletal impact of thyroid hormones, representing an important area for future investigation. Our multivariable MR analysis extends this understanding by demonstrating that the risk for primary osteoporosis and pathological fracture remains significant even after accounting for genetic predisposition to hypothyroidism. This suggests a direct, independent effect of thyroid hormone excess on bone fragility, which is consistent with clinical studies linking even subclinical hyperthyroidism to lower BMD and higher fracture risk [40, 41].

The reversal of the antidiabetic drug association after adjusting for T2D in our MVMR analysis highlights profound confounding by indication. Although T2D patients may have altered bone material strength [42] and some drugs like metformin may appear beneficial in unadjusted analyses [43, 44], our findings clarify that any observed benefit likely reflects improved metabolic control rather than a direct skeletal effect. This underscores that the relationship between antidiabetic therapy and bone health is complex and dominated by the underlying metabolic state.

RA is a chronic autoimmune disease with an increasing global burden, which induces systemic inflammation and cytokine release that inhibit bone formation [45]. For immunosuppressants, the attenuation of associations after controlling for RA in MVMR supports a disease-related rather than pharmacologic effect. This aligns with the established view that these inflammatory processes are primary drivers of bone loss, effects which may outweigh direct drug toxicity [46]. Our results thus suggest that the osteoporosis risk in these patients largely reflects the underlying inflammatory disease burden.

Limitations

Several limitations of this study should be considered. First, the generalizability of our findings may be limited as all genetic data were from European-ancestry populations. Second, medication-use exposures were based on self-report, lacking dosage and duration information, which prevents

dose-response assessment and may introduce measurement error. Third, as an MR study, our estimates reflect the effect of genetic predisposition to long-term medication use, not the effect of initiating a specific pharmacologic intervention. Fourth, despite sensitivity analyses, residual confounding from pleiotropy cannot be entirely excluded. Finally, our outcomes were confined to the osteoporosis phenotypes available in FinnGen; incorporating bone imaging parameters in the future would deepen the biological interpretation.

Conclusion

In conclusion, this Mendelian randomization study provides genetic evidence that the predisposition to use specific medications is associated with altered osteoporosis risk. We found that anilide and thyroid hormone use may independently increase the risk of osteoporosis and related fractures. In contrast, the apparent protective association of antidiabetic drugs was not sustained after accounting for type 2 diabetes, highlighting the critical role of confounding by indication. These findings underscore that medication-related skeletal fragility is an important consideration in clinical practice. Specifically, they suggest that patients on long-term paracetamol (anilide) or thyroid hormone therapy may benefit from proactive bone health monitoring. By systematically evaluating multiple drug classes and employing multivariable MR to disentangle direct effects from disease confounding, this study demonstrates a robust genetic epidemiological framework for post-marketing drug safety assessment. Future research incorporating diverse populations, precise prescription data, and detailed bone imaging phenotypes will be valuable to translate these genetic insights into personalized clinical strategies for osteoporosis prevention.

Declarations

Ethics approval and consent to participate

This study used only publicly available, de-identified GWAS summary statistics. All original studies received ethical approval from their respective institutional review boards, and informed consent was obtained from participants. No additional ethical approval or consent was required for the present analyses.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yuxuan Wu and Xi Chen carried out the studies, participated in collecting data, and drafted the manuscript. Xue Chen and Ran Hao performed the statistical analysis and participated in its design. Zhicong Wang participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Not applicable

Abbreviations

3-Hydroxy-3-methylglutaryl–coenzyme A, HMG-CoA

Advanced glycation end-products, AGEs

Anatomical Therapeutic Chemical Classification System, ATC

Bone mineral density, BMD

Coefficient of determination, R^2

Confidence interval, CI

Cyclooxygenase, COX

False discovery rate, FDR

Gastro-oesophageal reflux disease, GORD

Genome-wide association study, GWAS

GWAS Catalog Study ID, GCST

Instrumental variable, IV

International Classification of Diseases, ICD

Inverse variance-weighted, IVW

Leave-one-out, LOO

Linkage disequilibrium, LD

Mendelian Randomization Pleiotropy RESidual Sum and Outlier, MR-PRESSO

Mendelian randomization, MR

Minor allele frequency, MAF

Million Veteran Program, MVP

Multivariable Mendelian randomization, MVMR

Odds ratio, OR

Phenotype code, Phe

Prostaglandin E_2, PGE_2

Receptor activator of nuclear factor κB ligand, RANKL

Rheumatoid arthritis, RA

Single-nucleotide polymorphism, SNP

Sodium–glucose cotransporter 2, SGLT2

Standard error, SE

Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization, STROBE-MR

Type 2 diabetes, T2D

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Figure legends

Figure 1. Flowchart of the Mendelian randomization study design. The schematic illustrates the three-phase analytical workflow, encompassing instrumental variable selection and harmonization, univariable and multivariable MR analyses, and sensitivity validation.

Figure 2. Scatter plots of SNP-specific causal estimates for significant associations between medication use and osteoporosis-related outcomes. Each plot presents the association between a medication-use trait and an osteoporosis outcome (FDR < 0.05). The slope of each line represents the causal estimate from a different MR method. (A) Anilide use–osteoporosis, (B) Antidiabetic drug use–osteoporosis, (C) Immunosuppressant use–osteoporosis with pathological fracture, (D) Immunosuppressant use–drug-induced osteoporosis, (E) Thyroid preparation use–osteoporosis, (F) Thyroid preparation use–drug-induced osteoporosis, and (G) Thyroid preparation use–osteoporosis with pathological fracture.

Supplementary figures

Figure S1. Forest plots showing SNP-specific and pooled MR estimates for significant medication–osteoporosis associations. Each horizontal line represents the effect size and 95% confidence interval for a single SNP (FDR < 0.05). Panels (A–G) correspond to the same exposure–outcome pairs described in Figure 2.

Figure S2. Funnel plots assessing heterogeneity and directional pleiotropy for medication–osteoporosis associations. Each dot represents an individual SNP, plotted against its precision (1/SE). The symmetrical shape of the funnels suggests the absence of directional pleiotropy. Panels (A–G) correspond to associations with FDR < 0.05.

Figure S3. Leave-one-out (LOO) analyses for significant medication–osteoporosis associations. Each point represents the MR estimate recalculated after excluding one SNP at a time (FDR < 0.05). The stability of effect estimates across all iterations indicates that no single variant disproportionately influenced the overall causal estimates. Panels (A–G) correspond to the same exposure–outcome pairs described in Figure 2.

Table 1. Summary of GWAS datasets for medication-use exposures, osteoporosis-related outcomes, and covariates included in the Mendelian randomization analysis

ID	Trait(s)	Case (n)	Control (n)	Total Sample (n)	Category	Corresponding Exposure
GCST007922	Peptic ulcer and GORD drug use measurement			132367	Exposure	
GCST007923	Drugs used in diabetes use measurement			305913	Exposure	Type 2 diabetes (Phe_250_2)
GCST007924	Antithrombotic agent use measurement			153639	Exposure	
GCST007925	Vasodilators used in cardiac diseases use measurement			242659	Exposure	
GCST007926	Antihypertensive use measurement			152380	Exposure	
GCST007927	Beta blocking agent use measurement			224024	Exposure	
GCST007928	Diuretic use measurement			229086	Exposure	
GCST007929	Calcium channel blocker use measurement			204378	Exposure	

GCST007930	Agents acting on the renin–angiotensin system use measurement	237530	Exposure	
GCST007931	HMG CoA reductase inhibitor use measurement	290385	Exposure	
GCST007932	Thyroid preparation use measurement	305582	Exposure	Hypothyroidism (Phe_244)
GCST007933	Immunosuppressant use measurement	272602	Exposure	Rheumatoid arthritis (Phe_714_1)
GCST007934	Non-steroidal anti-inflammatory and antirheumatic product use measurement	164520	Exposure	
GCST007936	Opioid use measurement	78808	Exposure	
GCST007937	Aspirin (salicylic acid and derivatives) use measurement	112010	Exposure	
GCST007938	Anilide use measurement	179810	Exposure	Back pain (Phe_760)

GCST007939	Antimigraine preparation use measurement			119844	Exposure
GCST007940	Antidepressant use measurement			304162	Exposure
GCST007941	Inhalant adrenergic use measurement			176445	Exposure
GCST007942	Glucocorticoid use measurement			205700	Exposure
GCST007943	Antihistamine use measurement			151636	Exposure
GCST007944	Antiglaucoma preparations and miotics use measurement			100868	Exposure
M13_OSTEOPOROSIS	Osteoporosis	10461	47326 4	483725	Outcome
OSTEOPOROSIS_FRACTURE_FG	Osteoporosis with pathological fracture	2429	37431 7	376746	Outcome
ST19_FRACT_FEMUR	Fracture of femur	12229	47687 7	489106	Outcome
ST19_FRACT_LUMBAR_SPINE_PELVIS	Fracture of lumbar spine and pelvis	9061	48163 9	490700	Outcome

M13_ARTHROSIS_COX	Coxarthrosis	30802	31511	345917	Outcome	
DRUGADVERS_OSTEOPO	Drug-induced osteoporosis	389	49995	500348	Outcome	
Phe_250_2	Type 2 diabetes	154194	27845	432648	Covariate (MVP)	Drugs used in diabetes
Phe_244	Hypothyroidism	62814	37832	441135	Covariate (MVP)	Thyroid preparation
Phe_714_1	Rheumatoid arthritis	10479	43616	446640	Covariate (MVP)	Immunosuppressant
Phe_760	Back pain	218071	18506	403139	Covariate (MVP)	Anilide

Abbreviations: GWAS, genome-wide association study; MR, Mendelian randomization; MVP, Million Veteran Program; Phe, phenotype code from MVP; GORD, gastro-oesophageal reflux disease; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

All exposure data were obtained from the UK Biobank medication-use GWAS by Wu et al. (Nat Med, 2019). Osteoporosis-related outcome data were derived from the FinnGen R12 release, and covariate data were obtained from the Million Veteran Program (MVP).

"Corresponding exposure" indicates the medication–disease pairing used in multivariable MR analyses to adjust for underlying indications.

Table 2. Univariable Mendelian randomization estimates for the associations between medication use and osteoporosis-related outcomes

Exposure	Outcome	nSNP	Method	OR (95% CI)	P-value	FDR
Anilide	Osteoporosis	36	Inverse variance weighted	1.2541 (1.0895 - 1.4435)	0.0016	0.0201
Drugs used in diabetes	Osteoporosis	47	Inverse variance weighted	0.8846 (0.8385 - 0.9332)	6.95×10^{-6}	2.00×10^{-4}
Immunosuppressant	Osteoporosis with pathological fracture	25	Inverse variance weighted	1.1602 (1.0681 - 1.2602)	4.00×10^{-4}	0.0074
Immunosuppressant	Drug-induced osteoporosis	26	Inverse variance weighted	1.3617 (1.1294 - 1.6418)	0.0012	0.0168

Thyroid preparation	Osteoporosis	107	Inverse variance weighted	1.0761 (1.0378 - 1.1157)	7.16×10^{-5}	0.0016
Thyroid preparation	Drug-induced osteoporosis	109	Inverse variance weighted	1.3730 (1.1698 - 1.6115)	1.00×10^{-4}	0.0021
Thyroid preparation	Osteoporosis with pathological fracture	109	Inverse variance weighted	1.1167 (1.0455 - 1.1928)	0.001	0.0158
Anilide	Fracture of femur	36	Inverse variance weighted	1.2084 (1.0557 - 1.3831)	0.006	0.0601
Anilide	Coxarthrosis	28	Inverse variance weighted	1.1746 (1.0373 - 1.3300)	0.0111	0.1025

Antimigraine preparation	Coxarthrosis	11	Inverse variance weighted	1.0610 (1.0111 - 1.1134)	0.016	0.130 1
Antithrombotic agent	Coxarthrosis	11	Inverse variance weighted	0.8734 (0.7759 - 0.9832)	0.0251	0.192 3
Drugs used in diabetes	Coxarthrosis	43	Inverse variance weighted	0.9561 (0.9221 - 0.9914)	0.0152	0.130 1
Glucocorticoid	Fracture of femur	18	Inverse variance weighted	1.0972 (1.0089 - 1.1932)	0.0303	0.208 9
HMG CoA reductase inhibitor	Osteoporosis	65	Inverse variance weighted	0.8879 (0.8177 - 0.9641)	0.0047	0.053 5

Immunosuppressant	Fracture of femur	26	Inverse variance weighted	1.0527 (1.0148 - 1.0920)	0.0061	0.060 1
Inhalant adrenergic	Osteoporosis with pathological fracture	50	Inverse variance weighted	1.1445 (1.0135 - 1.2925)	0.0295	0.208 9
Inhalant adrenergic	Drug-induced osteoporosis	50	Inverse variance weighted	1.3829 (1.0243 - 1.8669)	0.0343	0.225 1
Non-steroidal anti-inflammatory and antirheumatic product	Osteoporosis with pathological fracture	7	Inverse variance weighted	2.0261 (1.0394 - 3.9495)	0.0381	0.239 2

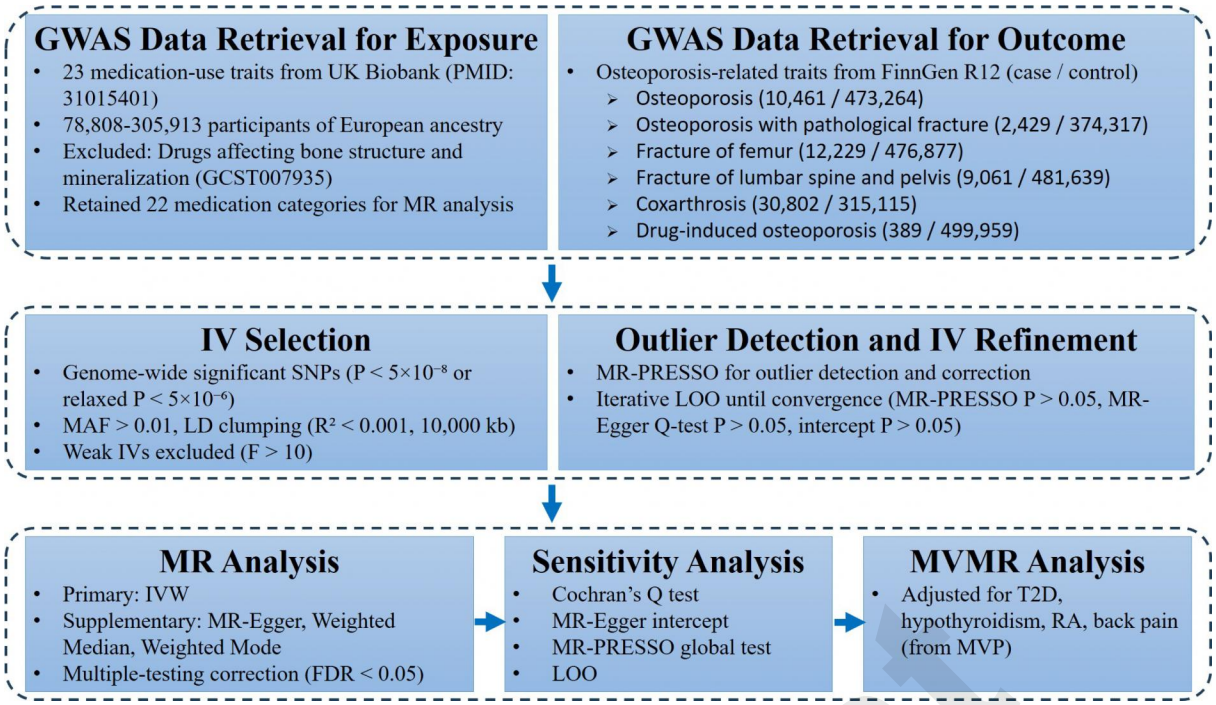
Estimates are derived from inverse variance–weighted (IVW) analyses using genome-wide significant and linkage-disequilibrium–independent SNPs as instrumental variables. Odds ratios (OR) represent the effect of genetically predicted medication use on the specified outcome. FDR, false discovery rate, was calculated using the Benjamini–Hochberg method.

Table 3. Multivariable Mendelian randomization (MVMR) estimates for the associations between medication use and osteoporosis-related outcomes after adjustment for corresponding disease indications.

Exposure	Outcome	Multivariables	OR (95% CI)	P-value
Anilide	Osteoporosis	Back pain	1.2506 (1.0589-1.4769)	0.0084
Drugs used in diabetes	Osteoporosis	Type 2 diabetes	1.1343 (1.0334-1.2450)	0.008
Thyroid preparation	Osteoporosis	Hypothyroidism	1.1434 (1.0766-1.2145)	1.30×10^{-5}
Thyroid preparation	Osteoporosis with pathological fracture	Hypothyroidism	1.1735 (1.0522-1.3087)	0.004
Thyroid preparation	Drug-induced osteoporosis	Hypothyroidism	1.2739 (0.9493-1.7094)	0.1067
Immunosuppressant	Osteoporosis with pathological fracture	Rheumatoid arthritis	0.9597 (0.8486-1.0853)	0.5121
Immunosuppressant	Drug-induced osteoporosis	Rheumatoid arthritis	1.0847 (0.8458-1.3911)	0.522

Abbreviations: OR, odds ratio; CI, confidence interval.

Estimates were derived using MVMR analyses adjusting for the underlying disease traits corresponding to each medication exposure (type 2 diabetes, hypothyroidism, rheumatoid arthritis, or back pain). Odds ratios represent the effect of genetically predicted medication use on osteoporosis-related outcomes independent of these confounders.


GWAS Data Retrieval for Exposure
23 medication-use traits from UK Biobank (PMID: 31015401)
78,808-305,913 participants of European ancestry
Excluded: Drugs affecting bone structure and mineralization (GCST007935)
Retained 22 medication categories for MR analysis
GWAS Data Retrieval for Outcome
Osteoporosis-related traits from FinnGen R12 (case / control)
Osteoporosis (10,461 / 473,264)
Osteoporosis with pathological fracture (2,429 / 374,317)
Fracture of femur (12,229 / 476,877)
Fracture of lumbar spine and pelvis (9,061 / 481,639)
Coxarthrosis (30,802 / 315,115)
Drug-induced osteoporosis (389 / 499,959)
IV Selection
Genome-wide significant SNPs (P < 5×10⁻⁸ or relaxed P < 5×10⁻⁶)
MAF > 0.01, LD clumping (R² < 0.001, 10,000 kb)
Weak IVs excluded (F > 10)
Outlier Detection and IV Refinement
MR-PRESSO for outlier detection and correction
Iterative LOO until convergence (MR-PRESSO P > 0.05, MR-Egger Q-test P > 0.05, intercept P > 0.05)
MR Analysis
Primary: IVW
Supplementary: MR-Egger, Weighted Median, Weighted Mode
Multiple-testing correction (FDR < 0.05)
Sensitivity Analysis
Cochran's Q test
MR-Egger intercept
MR-PRESSO global test
LOO
MVMR Analysis
Adjusted for T2D, hypothyroidism, RA, back pain (from MVP)

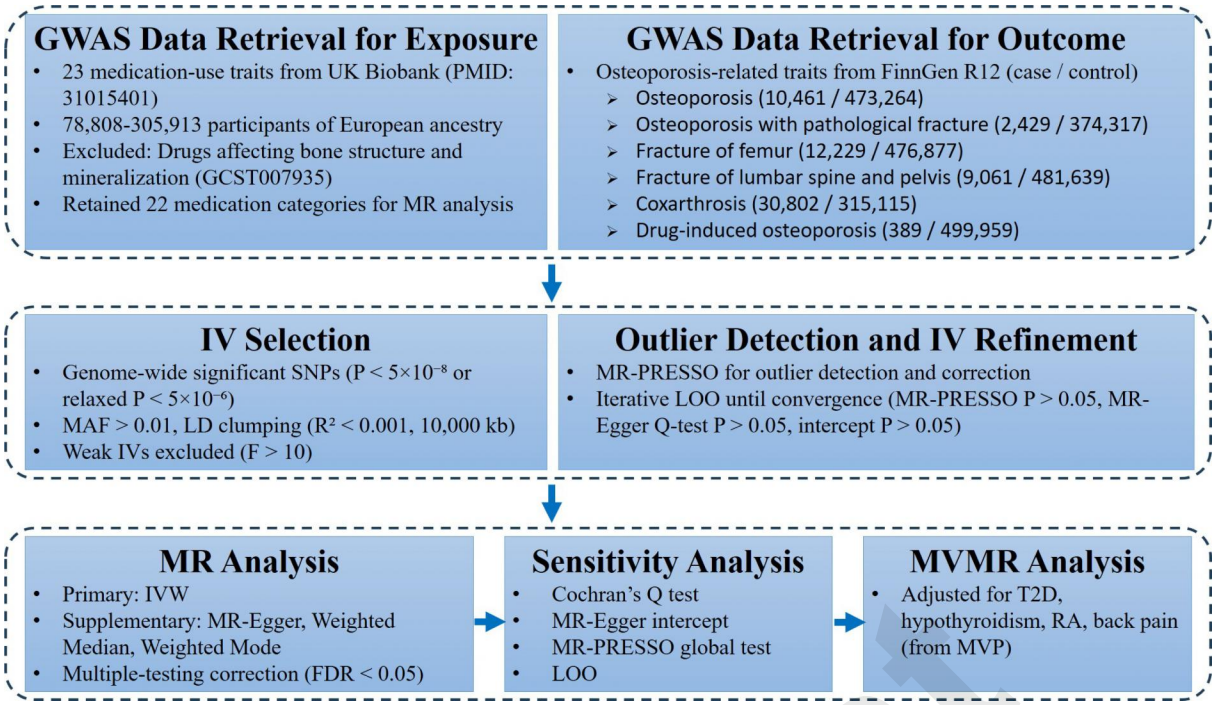


Figure 1. Overview of the study design. Summary-level data for 22 medication-use traits from the UK Biobank and osteoporosis-related outcomes from the FinnGen R12 cohort were analyzed using Mendelian randomization (MR). Independent single-nucleotide polymorphisms (SNPs) were selected as instrumental variables, followed by outlier correction, causal effect estimation, and sensitivity analyses. Multivariable MR (MCMR) was further performed to account for disease-related confounding. GWAS, genome-wide association study; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; SNP, single nucleotide polymorphism; IV, instrumental variable; IVW, inverse variance–weighted; LD, linkage disequilibrium; LOO, leave-one-out; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; T2D, type 2 diabetes; RA, rheumatoid arthritis.

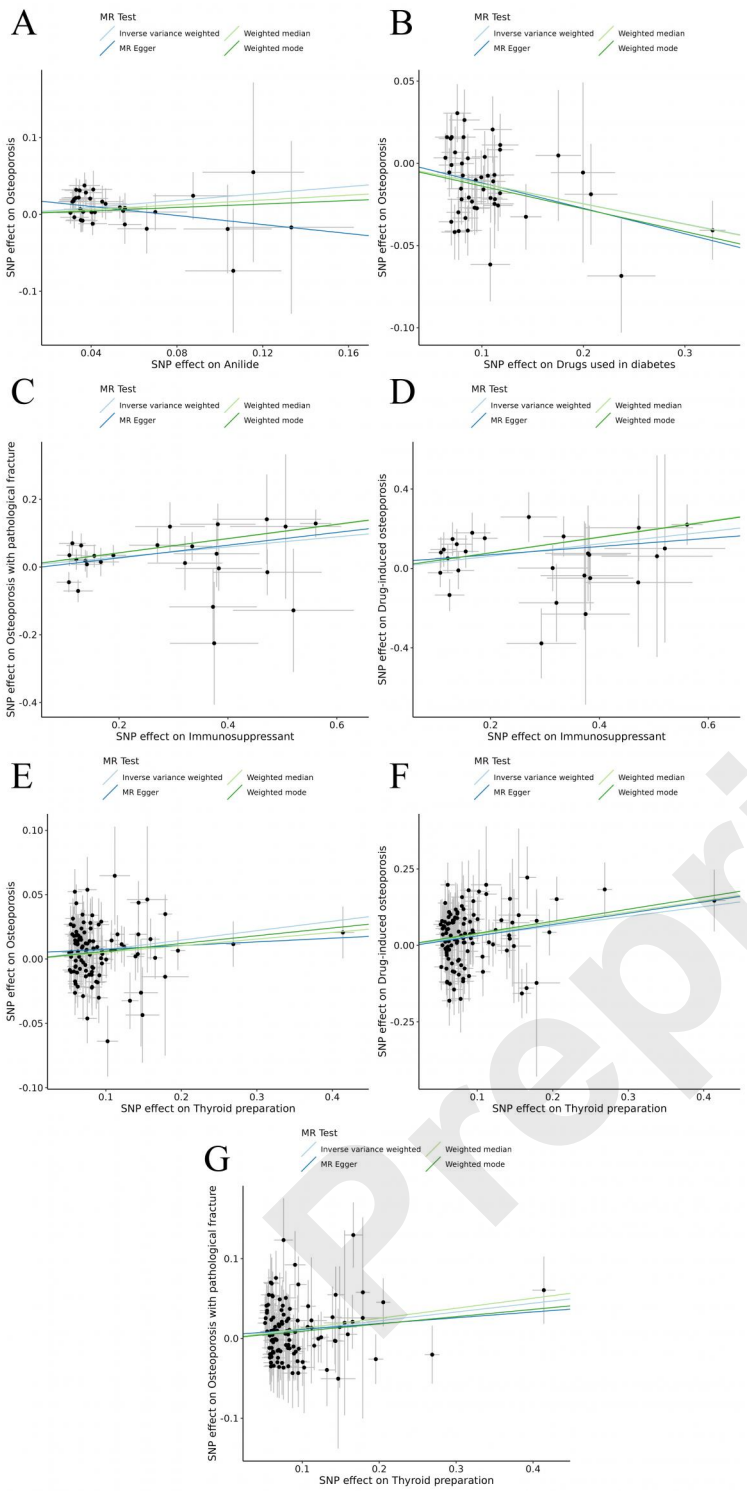


Figure 2. Scatter plots of SNP-specific causal estimates for significant associations between medication use and osteoporosis-related outcomes (FDR < 0.05). Each point represents an individual SNP, with slopes indicating causal estimates derived from different MR methods (IVW, MR-Egger, weighted median, and weighted mode). (A) Anilide use–osteoporosis, (B) Antidiabetic drug use–osteoporosis, (C) Immunosuppressant use–osteoporosis with pathological fracture, (D) Immunosuppressant use–drug-induced osteoporosis, (E) Thyroid preparation use–osteoporosis, (F) Thyroid preparation use–drug-induced osteoporosis, and (G) Thyroid preparation use–osteoporosis with pathological fracture.