Basic research

Rheumatology

Genetic associations between common medication use and osteoporosis-related outcomes: a Mendelian randomization study

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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 higher odds of osteoporosis (OR = 1.25, FDR = 0.0201); immunosuppressant use with higher odds 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 odds of 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 association reversed after adjustment for type 2 diabetes, suggesting that the inverse association may reflect the underlying metabolic condition rather than a direct pharmacological effect.

Conclusions: Genetic evidence suggests that anilide and thyroid hormone use may independently increase osteoporosis risk, while the inverse association between antidiabetic drug use and osteoporosis may be 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.

Introduction

Osteoporosis is a chronic metabolic bone disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to

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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 a major cause of iatrogenic osteoporosis, with fractures occurring in up to 30–50% of patients receiving chronic treatment [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 through increased bone turnover [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 an approach to investigate potential causal 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 highlights the need for 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], including the potential for personalized medication decisions and 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 investigate associations conditional on underlying disease indications. By integrating this dual analytical framework across diverse drug categories and phenotypes, our work provides genetic evidence on associations between medication-related traits and osteoporosis risk, with the ultimate goal of guiding safer prescribing practices and targeted bone health monitoring.

Material and methods

Study design

This study followed a predefined, stepwise analytical plan to assess the potential causal effects of medication use on 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 indication-related conditions (e.g., type 2 diabetes, back pain; Million Veteran Program). For each trait, independent single-nucleotide polymorphisms (SNPs) meeting genome-wide significance ($p < 5 \times 10^{-8}$) and linkage disequilibrium ($R^2 < 0.001$) criteria were selected as IVs, based on the assumptions underlying MR [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 overall association. The primary 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 investigate the association of medication use with osteoporosis conditional on the underlying disease indication, we performed MVMR. For each significant or candidate medication, such as anilides and thyroid drugs, we includ-

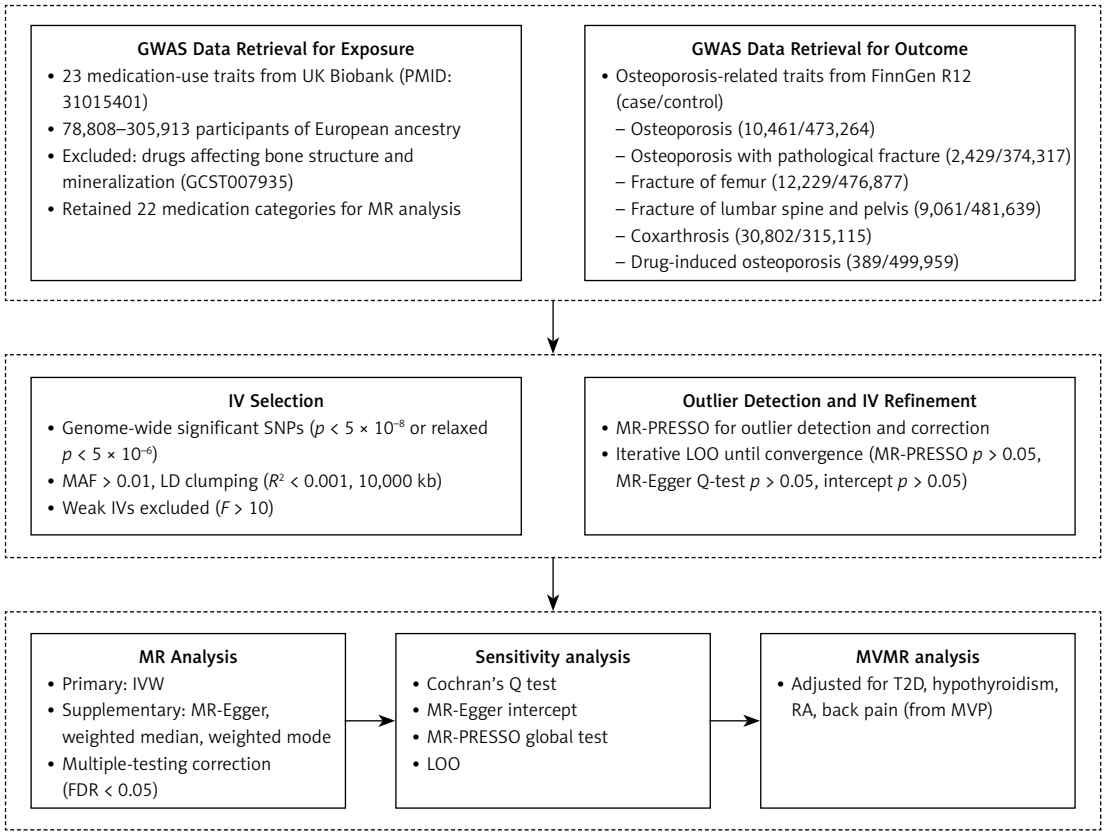

Figure 1. Flowchart of the Mendelian randomization study design. The schematic illustrates the three-phase analytical workflow, encompassing instrumental variable selection and harmonization, univariable and multivariable MR analyses, and sensitivity validation

ed the genetic instruments for both the medication and its corresponding indication disease such as back pain or hypothyroidism in a joint model using the multivariable IVW method.

Step 4. Sensitivity and robustness analyses. 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 the MR-Egger intercept and MR-PRESSO global tests; and (iii) conducting leave-one-out (LOO) analyses to assess whether the results were 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 the medication-use trait for drugs affecting bone structure and mineralization (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), correspond-

ing, respectively, to antidiabetic, thyroid, immunosuppressant, and anilide exposures.

All included traits are summarized in Table I. 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 (DOI: 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, a 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 associations between each medication-use trait and osteoporosis-related outcomes were estimated using four complementary MR models: 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

Table I. 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 size (*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	

Table I. Cont.

ID	Trait(s)	Case (*n*)	Control (*n*)	Total sample size (*n*)	Category	Corresponding 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	473264	483725	Outcome	
OSTEOPOROSIS_FRACTURE_FG	Osteoporosis with pathological fracture	2429	374317	376746	Outcome	
ST19_FRACT_FEMUR	Fracture of femur	12229	476877	489106	Outcome	
ST19_FRACT_LUMBAR_SPINE_PELVIS	Fracture of lumbar spine and pelvis	9061	481639	490700	Outcome	
M13_ARTHROSIS_COX	Coxarthrosis	30802	315115	345917	Outcome	
DRUGADVERS_OSTEOPO	Drug-induced osteoporosis	389	499959	500348	Outcome	
Phe_250_2	Type 2 diabetes	154194	278454	432648	Covariate (MVP)	Drugs used in diabetes
Phe_244	Hypothyroidism	62814	378321	441135	Covariate (MVP)	Thyroid preparation
Phe_714_1	Rheumatoid arthritis	10479	436161	446640	Covariate (MVP)	Immunosuppressant
Phe_760	Back pain	218071	185068	403139	Covariate (MVP)	Anilide

GWAS – genome-wide association study, MR – Mendelian randomization, MVP – Million Veteran Program, Phe – phenotype code from MVP, GORD – gastroesophageal 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.

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 [22, 24].

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 [25]. 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 conditional associations of each exposure while accounting for correlated traits [26].

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 [27]. 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 a rapid reduction of bone mineral density and deterioration of trabecular microstructure [28], 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 evaluate the influence of horizontal pleiotropy and individual SNPs on the estimates, SNPs identified as outliers or influential variants were excluded through a two-step procedure: (1) initial outlier detection using the MR-PRESSO framework, followed by (2) an iterative LOO analysis for pairs where heterogeneity persisted. The iterative procedure continued until the estimates satisfied the prespecified criteria for heterogeneity and directional pleiotropy (all $p > 0.05$). The list of excluded SNPs is detailed in Supplementary Table SI. After exclusion, all retained IVs satisfied the predefined 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 higher odds of osteoporosis (OR = 1.25, 95% CI: 1.09–1.44, FDR = 0.0201); immunosuppressant use with higher odds 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 odds 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 osteoporo-

sis (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, 3-Hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors, immunosuppressants, and inhalant adrenergics with osteoporosis and related skeletal disorders (Table II). Results from supplementary MR methods (MR-Egger, weighted median, and weighted mode) were largely consistent in direction and magnitude with the IVW estimates (Supplementary Table SII). The scatter (Figure 2) and forest plots (Supplementary Figure S1) for FDR-significant associations demonstrated broad agreement between the SNP-specific estimates and the overall MR estimates across methods. The corresponding funnel and LOO plots showed approximately symmetric distributions, with no clear evidence of influential individual variants (Supplementary Figures S2 and S3).

Table II. 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	0.1301
Antithrombotic agent	Coxarthrosis	11	Inverse variance weighted	0.8734 (0.7759–0.9832)	0.0251	0.1923
Drugs used in diabetes	Coxarthrosis	43	Inverse variance weighted	0.9561 (0.9221–0.9914)	0.0152	0.1301
Glucocorticoid	Fracture of femur	18	Inverse variance weighted	1.0972 (1.0089–1.1932)	0.0303	0.2089
HMG-CoA reductase inhibitor	Osteoporosis	65	Inverse variance weighted	0.8879 (0.8177–0.9641)	0.0047	0.0535
Immunosuppressant	Fracture of femur	26	Inverse variance weighted	1.0527 (1.0148–1.0920)	0.0061	0.0601
Inhalant adrenergic	Osteoporosis with pathological fracture	50	Inverse variance weighted	1.1445 (1.0135–1.2925)	0.0295	0.2089
Inhalant adrenergic	Drug-induced osteoporosis	50	Inverse variance weighted	1.3829 (1.0243–1.8669)	0.0343	0.2251
Non-steroidal anti-inflammatory and antirheumatic product	Osteoporosis with pathological fracture	7	Inverse variance weighted	2.0261 (1.0394–3.9495)	0.0381	0.2392

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 associations between genetically predicted medication use and the specified outcome. FDR – false discovery rate, was calculated using the Benjamini–Hochberg method.

Sensitivity analyses

Sensitivity analyses were conducted to assess heterogeneity and horizontal pleiotropy for all exposure–outcome pairs after outlier correction. As shown in Supplementary Table SIII, 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 statistically significant evidence of residual horizontal pleiotropy ($p > 0.05$) in any exposure–outcome combination (Supplementary Table SIV). These findings indicate that the IVs used in the MR analyses showed no statistically significant evidence of heterogeneity or directional pleiotropy in the applied diagnostic tests.

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 III, the associations of anilide use with higher odds of 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, $p = 1.3 \times 10^{-5}$) and osteoporosis with pathological fracture (OR = 1.17, 95% CI: 1.05–1.31, $p = 0.004$)

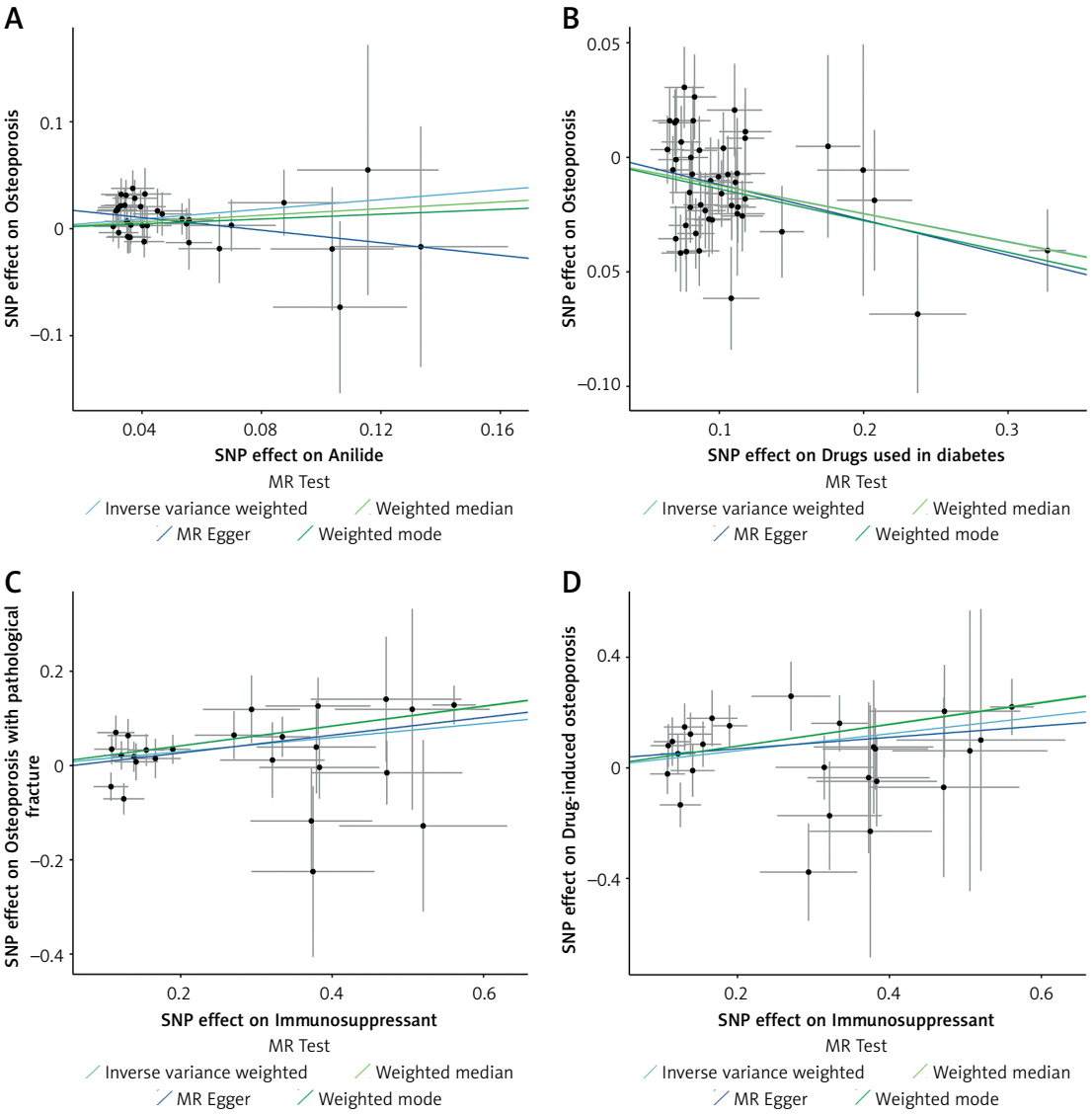

Figure 2. Scatter plots of SNP-specific causal estimates for significant associations between medication use and osteoporosis-related outcomes. Each plot presents the association between a medication-use trait and an osteoporosis outcome (FDR < 0.05). The slope of each line represents the causal estimate 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

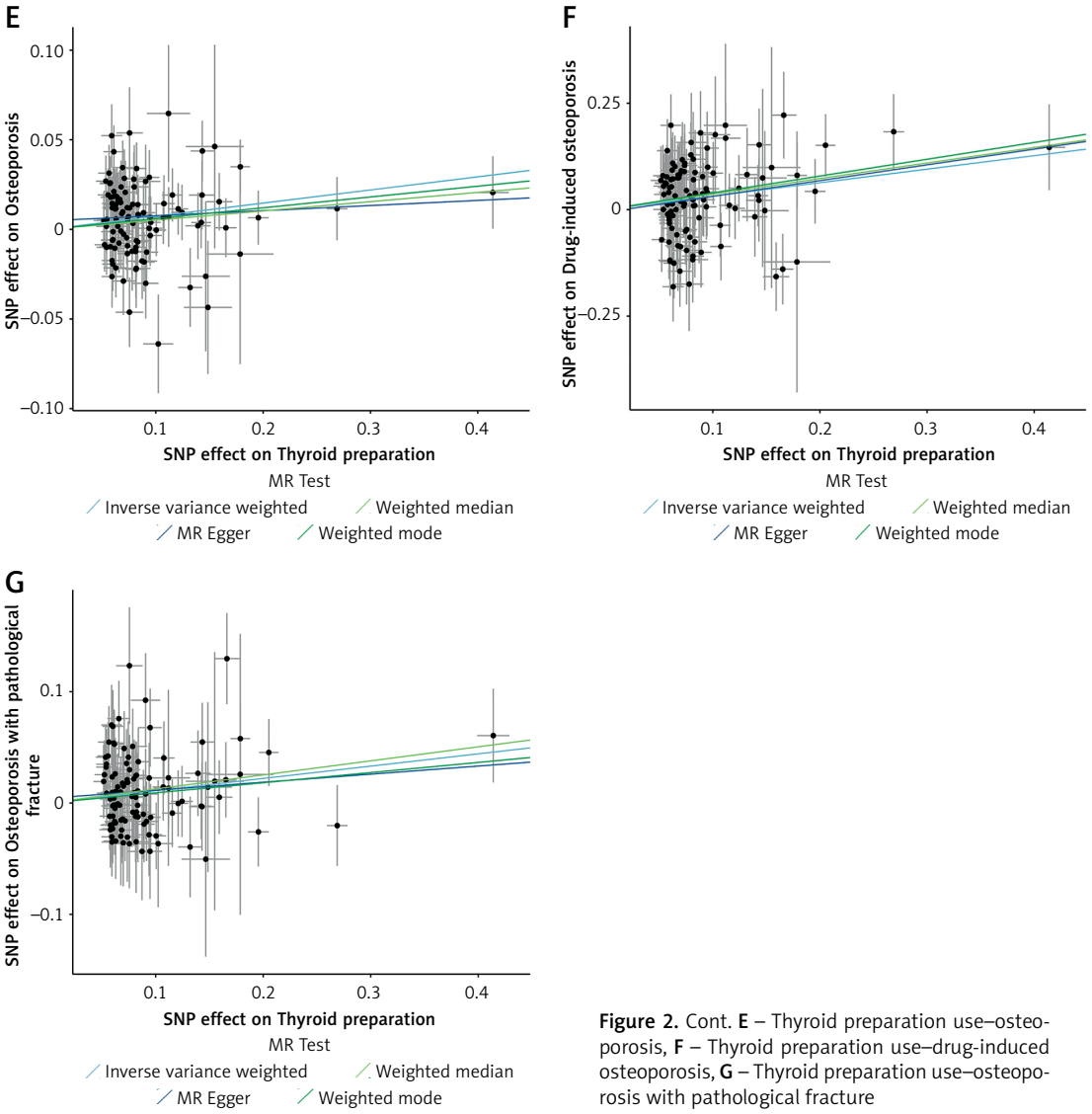

Figure 2. Cont. **E** – Thyroid preparation use–osteoporosis, **F** – Thyroid preparation use–drug-induced osteoporosis, **G** – Thyroid preparation use–osteoporosis with pathological fracture

Table III. 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

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 associations between genetically predicted medication use and osteoporosis-related outcomes conditional on these disease traits.

remained significant after controlling for back pain and hypothyroidism, respectively. In contrast, the previously inverse association between antidiabetic drug use and osteoporosis in univariable MR reversed after adjustment for T2D (OR = 1.13, 95% CI: 1.03–1.25, $p = 0.008$), suggesting that the inverse association may have reflected the genetic association with the underlying disease rather than an association with medication use independent of T2D. Similarly, the associations of thyroid preparations and immunosuppressants with drug-induced osteoporosis, and immunosuppressant use with osteoporosis with pathological fracture, were no longer statistically significant after controlling for hypothyroidism or RA, respectively.

Discussion

In this study, MR and MVMR analyses identified associations of anilide use with increased osteoporosis risk and thyroid preparations with higher risks of osteoporosis and osteoporosis with pathological fracture [29, 30]. The inverse association between antidiabetic drug use and osteoporosis in univariable MR was reversed after adjusting for T2D, suggesting that the association may depend on accounting for the underlying disease indication [31]. 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 [32]. These findings suggest that medication-use traits may be associated with skeletal outcomes, but do not establish that prolonged use of these medications increases bone fragility or justify specific monitoring recommendations on their own.

By integrating univariable and multivariable MR approaches [33], this study examined associations between medication-use traits and skeletal outcomes while accounting for selected 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, highlight the importance of accounting for disease indications when interpreting genetically inferred medication-use associations. This dual-level analysis provides complementary evidence, although it cannot definitively distinguish pharmacologic effects from disease-related influences. It also underscores the potential value of genetically predicted medication-use traits for evaluating drug safety at the population level.

Anilides, primarily paracetamol, are among the most commonly used analgesics [19, 34]. While epidemiological studies have associated their regular use with increased fracture risk [29], our Mendelian randomization analysis provides genetic evidence of an association between genetically predicted anilide use and osteoporosis, although a causal interpretation depends on the validity of the MR assumptions. The underlying mechanisms may involve the inhibition of bone-forming osteoblast activity through cyclooxygenase suppression, coupled with reduced mobility due to chronic pain [35, 36]. Therefore, our findings add to previous observational evidence linking anilide use with skeletal outcomes, but do not establish a pharmacological mechanism or demonstrate that long-term users require additional bone-health monitoring.

The observed association between thyroid preparation use and increased osteoporosis risk aligns with extensive evidence that thyroid hormones accelerate bone turnover [37]. 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 found that the associations with primary osteoporosis and pathological fracture remained significant after accounting for genetic predisposition to hypothyroidism. This is consistent with, but does not establish, an 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 [30, 38].

The reversal of the antidiabetic drug association after adjusting for T2D in our MVMR analysis suggests that the association depends on accounting for the underlying disease indication. Although T2D patients may have altered bone material strength [39] and some drugs like metformin may appear beneficial in unadjusted analyses [40, 41], our findings do not establish whether the association reflects metabolic control or a direct skeletal effect of medication. 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 [42]. For immunosuppressants, the attenuation of associations after controlling for RA in MVMR is consistent with a contribution from the underlying disease, although it does not exclude pharmacologic effects. This aligns with the established view that these inflammatory processes are primary drivers of bone loss, while the relative contributions of disease activity and medication effects remain uncertain [43]. Our results thus suggest that the osteoporosis risk in these patients may partly reflect the underlying inflammatory disease burden.

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 associations with genetic predisposition to medication use rather than the effects of initiating a specific pharmacologic intervention. Fourth, despite sensitivity analyses, horizontal pleiotropy and residual bias cannot be entirely excluded. Finally, our outcomes were confined to the osteoporosis phenotypes available in FinnGen; incorporating bone imaging parameters in the future would provide further insight into the underlying skeletal changes.

In conclusion, this Mendelian randomization study provides genetic evidence that the genetic predisposition to use specific medications is associated with altered osteoporosis risk. We found that anilide and thyroid hormone use may be associated with higher odds of osteoporosis and related fractures. In contrast, the inverse association between antidiabetic drugs and osteoporosis was not sustained after accounting for type 2 diabetes, highlighting the importance of accounting for the underlying disease indication. These findings suggest that medication-related skeletal fragility warrants further investigation. However, the findings alone do not establish a need for additional bone health monitoring in patients receiving long-term paracetamol (anilide) or thyroid hormone therapy. By systematically evaluating multiple drug classes and employing multivariable MR to examine associations conditional on disease indications, this study illustrates a potential framework for using genetic epidemiology to investigate drug safety. Future research incorporating diverse populations, precise prescription data, and detailed bone imaging phenotypes will be valuable for clarifying these associations and assessing their clinical implications for osteoporosis prevention.

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Ethical approval

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.

Conflict of interest

The authors declare no conflict of interest.

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