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Association of antihypertensive drugs with fracture and bone mineral density: A comprehensive drug-target Mendelian randomization study

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Background: Observational studies have investigated the associations between antihypertensive drugs and fracture risk as well as bone mineral density (BMD), but yielding controversial results.

Methods: In this study, a comprehensive drug-target Mendelian randomization (MR) analysis was conducted to systematically examine the associations between genetic proxies for eight common antihypertensive drugs and three bone health-related traits (fracture, total body BMD [TB-BMD], and estimated heel BMD [eBMD]). The main analysis used the inverse-variance weighted (IVW) method to estimate the causal effect. Multiple MR methods were also employed to test the robustness of the results.

Results: The genetic proxies for angiotensin receptor blockers (ARBs) were associated with a reduced risk of fracture (odds ratio [OR] = 0.67, 95% confidence interval [CI]: 0.54 to 0.84; $P = 4.42 \times 10^{-4}$; P-adjusted = 0.004), higher TB-BMD ($\beta = 0.36$, 95% CI: 0.11 to 0.61; $P = 0.005$; P-adjusted = 0.022), and higher eBMD ($\beta = 0.30$, 95% CI: 0.21 to 0.38; $P = 3.59 \times 10^{-12}$; P-adjusted = 6.55×10^{-11}). Meanwhile, genetic proxies for calcium channel blockers (CCBs) were associated with an increased risk of fracture (OR = 1.07, 95% CI: 1.03 to 1.12; $P = 0.002$; P-adjusted = 0.013). Genetic proxies for potassium sparing diuretics (PSDs) showed negative associations with TB-BMD ($\beta = -0.61$, 95% CI: -0.88 to -0.33; $P = 1.55 \times 10^{-5}$; P-adjusted = 1.86×10^{-4}). Genetic proxies for thiazide diuretics had positive associations with eBMD ($\beta = 0.11$, 95% CI: 0.03 to 0.18; $P = 0.006$; P-adjusted = 0.022). No significant heterogeneity or pleiotropy was identified. The results were consistent across different MR methods.

Conclusions: These findings suggest that genetic proxies for ARBs and thiazide diuretics may have a protective effect on bone health, while genetic proxies for CCBs and PSDs may have a negative effect.

1 Introduction

Blood pressure lowering through antihypertensive drugs is an established strategy for hypertension management to reduce the risk of developing cardiovascular diseases (1, 2). Hypertension and osteoporosis are often co-existed, especially in the aging population (3). The effects on osteoporosis from antihypertensive drugs can differ due to the diverse mechanisms of action among different classes of these drugs. The use of antihypertensive drugs should take the possible impact on bone health into account, so that the antihypertensive drugs benefiting bone health can be preferred.

The observational associations between antihypertensive drugs and fracture have been extensively studied, with the association direction and strength expected to be depended on the specific type of antihypertensive drug class. The cohort study in the Osteoporotic Fracture in Men Study (MrOS) reported that using angiotensin receptor blockers (ARBs) for prolonged periods reduced the risk of non-vertebral fractures in the elderly compared to using angiotensin-converting enzyme inhibitors (ACEIs) or calcium channel blockers (CCBs) (4). A recent meta-analysis illustrated that thiazide diuretics, beta-blockers (BBs), and ARBs could reduce the risk of hip fracture (5). Recent studies regarding the risk of falls in older adults have also raised concerns about hip fracture resulted from antihypertensive drug use (6, 7). However, the associations between different antihypertensive drugs and the occurrence of fracture remains largely inconsistent and controversial. These inconsistent findings may be attributed to differences in study populations and outcome definitions as well as bias due to unmeasured confounding. The observational design was commonly acknowledged to be insufficient to prove causality. Although randomized clinical trials (RCTs) are often regarded as the gold standard for determining causality, they can have limitations in terms of feasibility, cost, and ethics (8).

Mendelian randomization analysis has been developed as a powerful statistical method for assessing causal associations using genetic variables as instruments (9). Random assignment of genetic alleles effectively eliminates the effect of unobserved confounding factors and reduces measurement error, similar to randomization in RCTs (10). Given the wide availability of summary data from genome-wide association study (GWAS), MR could efficiently and economically assess the causal relationship between exposure and disease outcome (11). Drug-target MR can be used to predict drug development and repurposing opportunities by using genetic instruments in or near target genes to simulate the potential actions of drug targets (12).

In the present study, using single-nucleotide polymorphisms (SNPs) in or near drug target genes as drug genetic proxies, we conducted a comprehensive drug-target MR analysis systematically examining the causal associations between antihypertensive drug classes and bone health-related traits, including fractures, total body bone mineral density (TB-BMD), and estimated heel BMD (eBMD). The results can provide a helpful guide regarding the use of antihypertensive drugs, especially for those hypertension patients with poor bone health. In addition, the findings may promote the repurposing of antihypertensive drugs as a potential osteoporosis prevention strategy for future trial design.

2 Methods

2.1 Study design

We estimated the causal associations of genetic proxies for antihypertensive drugs with bone health-related traits by a drug-target MR method, with the study design provided in Figure 1. We totally included eight commonly used antihypertensive drugs following the guidelines of the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 (13), including alpha-blockers, ACEIs, ARBs, BBs, thiazide diuretics, loop diuretics, potassium sparing diuretics (PSDs), and CCBs. Specifically, we first identified genetic variants associated with blood pressure (BP) lowering in drug target genes to proxy drug target effects. Then, the causal effects of these drug genetic proxies on fracture, TB-BMD, and eBMD were evaluated using multiple MR methods. A completed Study to Enhance the Use of Mendelian Randomization for Observational Epidemiology (STROBE-MR) statement was provided (14) (Supplementary STROBE-MR checklist).

2.2 Data source

Data sources were detailed in Table 1. All the GWAS summary data were with European ancestry. The GWAS summary statistics of bone health-related traits were obtained from the GEnetic Factors for Osteoporosis Consortium website (GEFOS, http://www.gefos.org/). Studies with sample sizes greater than 50,000 in the GEFOS consortium were selected to improve statistical power, including fracture, TB-BMD, and eBMD. The GWAS summary
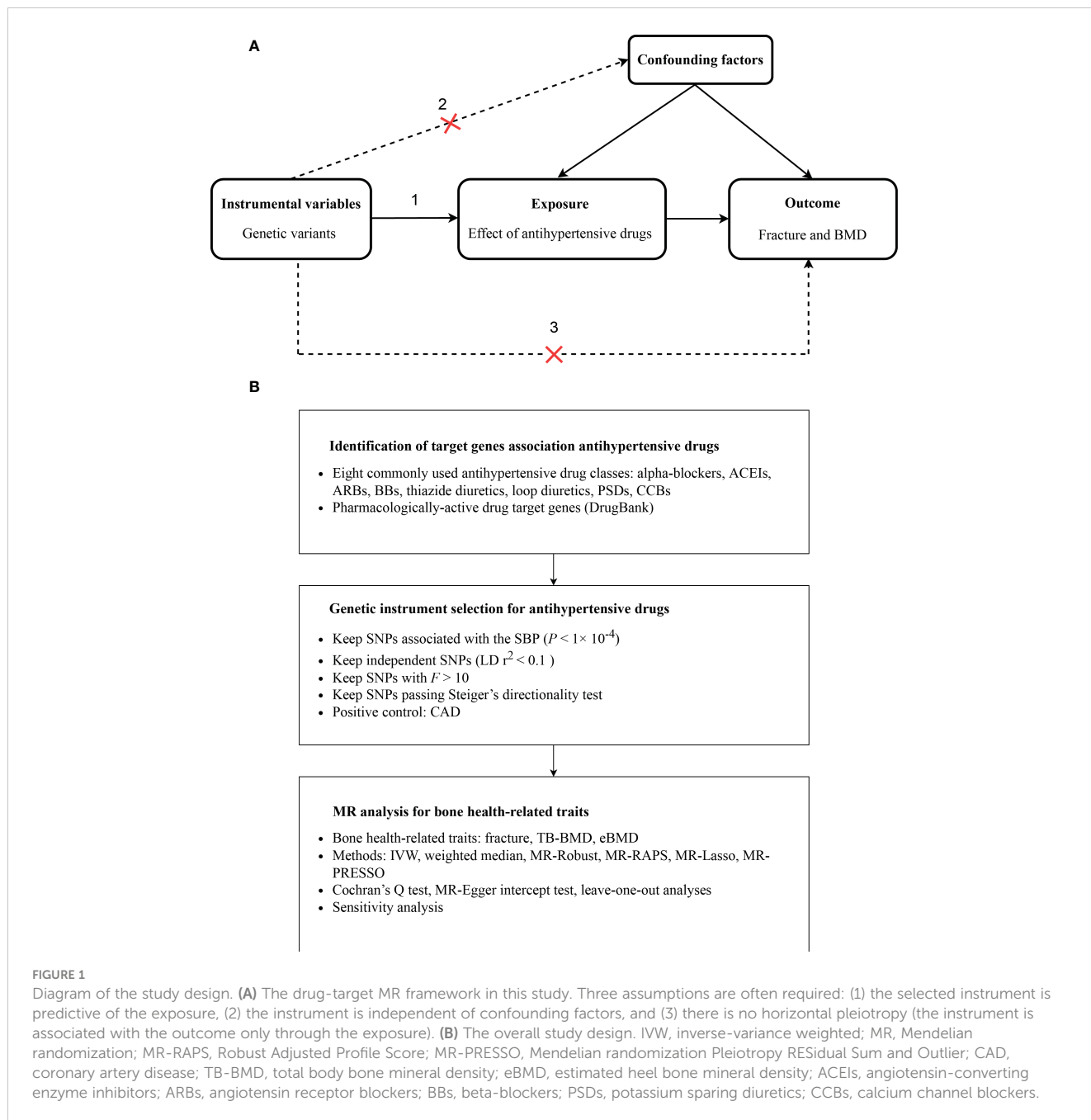
FIGURE 1

Diagram of the study design. **(A)** The drug-target MR framework in this study. Three assumptions are often required: (1) the selected instrument is predictive of the exposure, (2) the instrument is independent of confounding factors, and (3) there is no horizontal pleiotropy (the instrument is associated with the outcome only through the exposure). **(B)** The overall study design. IVW, inverse-variance weighted; MR, Mendelian randomization; MR-RAPS, Robust Adjusted Profile Score; MR-PRESSO, Mendelian randomization Pleiotropy RESidual Sum and Outlier; CAD, coronary artery disease; TB-BMD, total body bone mineral density; eBMD, estimated heel bone mineral density; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta-blockers; PSDs, potassium sparing diuretics; CCBs, calcium channel blockers.

TABLE 1 Summary of GWAS datasets included in this study.

Phenotype	Sample size (case/control)	Number of SNPs	Population	Adjustments[a]
Exposure				
SBP	757,601	7,088,083	European	Age, age^2, sex, BMI
Outcomes				
Fracture	416,795(53,184/373,611)	13,977,204	European	Age, sex
eBMD	426,824	13,681,377	European	Age, sex
TB-BMD	56,284	16,162,733	European	Age, weight
CAD	547,261(122,733/424,528)	7,934,254	European	Age, sex

GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; eBMD, estimated heel bone mineral density; TB-BMD, total body bone mineral density; SBP, systolic blood pressure; CAD, coronary artery disease; BMI, body mass index.
[a]All GWAS studies have further adjusted for principal components.

data for both fracture (53,184 cases and 373,611 controls) and eBMD (n = 426,824) were obtained from UKB with adjustment for sex, age, with the largest sample size to date [15]. Fracture was defined using ICD-10 diagnostic codes, where the codes for skull, face, hand and foot fractures, pathological fractures caused by malignant tumors, atypical femoral fractures, periprosthetic fractures and healed fractures were excluded. Summary-level data for eBMD was measured using quantitative ultrasound. The summary data of TB-BMD, were provided by a meta-analysis (n = 56,284), with adjustment for age, weight, height, and measured utilizing dual-energy X-ray absorptiometry (DXA) [16].

The GWAS summary data for systolic blood pressure (SBP) was from a meta-analysis of the International Consortium for Blood Pressure (ICBP) [17]. The GWAS was conducted using linear regression and combined across studies using inverse-variance weighted meta-analysis, including up to 757,601 participants with adjustment for age, age^2, sex, and BMI. The GWAS summary data of coronary artery disease (CAD) (122,733 cases and 424,528 controls), which we included here as a positive control to validate genetic instruments, was obtained from CARDIoGRAMplusC4D, with adjustment for sex and age [18].

2.3 Genetic instrument selection for antihypertensive drugs

We selected SNPs associated with blood pressure (BP) lowering in or near drug target genes as proxies for different antihypertensive drugs. Specifically, we identified eight commonly used antihypertensive drug classes and collected information on the protein targets of these drugs from the DrugBank [19]. We, following previous studies [20], selected SNPs in or near (± 200 kb) corresponding target genes as proxies for antihypertensive drug classes, if they are associated with SBP based on $P < 1 \times 10^{-4}$.

In addition, we estimated the F statistics of every instrument and only kept those variants with F > 10 to avoid weak instrumental bias [21]. We then clumped these SNPs according to a lenient linkage disequilibrium (LD) threshold of $r^2 < 0.1$ using the 1000 Genomes Project European reference panel. We employed MR Steiger filtering to exclude those genetic instruments which explained less variance on outcome than on exposure. Steiger filtering can infer the causal direction for an identified SNP between exposure and outcome through estimating and comparing the proportion of variance explained in each [22]. To validate the genetic proxies for antihypertensive drug instruments, we further examined the associations between genetically proxied antihypertensive drugs and CAD, and compared them with previous meta-analyses of clinical trials [23, 24], which can be used as positive control since antihypertensive drugs are known to have cardiovascular protective effects.

2.4 Statistical analysis

Prior to the MR analysis, summary data for the instruments on exposure and outcome were harmonized. When a SNP was missing

for the outcome association, a proxy ($r^2 \geq 0.8$) was sought for it, and those SNPs without proxies were further removed. Palindromic SNPs with moderate minor allele frequency (> 0.4) were removed, as allele reversal could not be inferred. Inverse variance weighting (IVW) was performed as the main MR analysis to obtain the estimate of the causal association. In addition, multiple MR methods with different model assumptions were used to evaluate the robustness and reliability of our findings, including (1) weighted median method, which is consistent if at least 50% of the weight comes from valid instrumental variables [25]; (2) IVW method using robust regression (MR-Robust), which can reduce the standard error of estimates [26]; (3) MR Robust Adjusted Profile Score (MR-RAPS), which is robust to both systematic and idiosyncratic pleiotropy [27]; (4) MR-Lasso, which uses penalization to identify the candidate instrumental SNPs [26]; (5) Mendelian randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis, which makes causal inference as well as outlier detection [28].

We used the R packages "MendelianRandomization" [29], "mr.raps" [27], and "MRPRESSO" [28] to conduct MR analyses. All the reported Odds ratios (OR) or causal effect estimates were corresponding to per 5 mmHg lower SBP to make the effect comparable. For the main analysis using IVW method, we chose a false discovery rate (FDR) method for multiple testing correction with the significance threshold being FDR adjust $P < 0.05$, in recognition that the Bonferroni correction for multiple non-independent tests may be too stringent. The nominally significant threshold ($P < 0.05$) was used for alternative MR methods. The P values after FDR correction were described as P-adjusted.

2.5 Sensitivity analysis

The MR-Egger method was used to check for potential pleiotropy by testing for a significantly deviating MR-Egger intercept from zero [30]. Heterogeneity was assessed using Cochran's Q statistics. Leave-one-out (LOO) analysis was carried out to test whether any single SNP contributed powerfully to the causal effects. In addition, we used the Phenoscanner tool [31, 32] to check whether any of the selected SNPs (or their proxies, $r^2 > 0.8$) were associated with other risk factors of bone health-related traits (such as body mass index, smoking, stroke) [33] at genome-wide significance as potential pleiotropy. We then removed the identified potentially pleiotropic SNPs for sensitivity analysis to determine the robustness of the results.

3 Results

3.1 Genetic instrument selection and validation

For eight different antihypertensive drug classes, we identified a total of 38 pharmacological target genes (Supplementary Table 1) and chose genetic instruments within or nearby drug targets genes as proxies. Totally, 120 SNPs were obtained following the strict

instrument screening procedure described above, with details provided in Figure 1. All of these instrumental SNPs had F statistics of more than 10, which suggests that the weak instrument bias was not expected to affect the results. Briefly, there were 12 SNPs for alpha-blockers, 5 for ACEIs, 4 for ARBs, 20 for BBs, 4 for thiazide diuretics, 9 for loop diuretics, 2 for PSDs, 64 for CCBs (Supplementary Table 2). Positive control results for the effects of genetic proxies of antihypertensive drugs on CAD were consistent with results from clinical trials, indicating the validity of these instrumental SNPs (Supplementary Figure 1).

3.2 Drug-target MR analysis for fracture

We first examined the causal effect of antihypertensive drugs on fracture risk using drug-target MR analysis (Figure 2; Supplementary Table 4). The genetic proxies for ARBs have shown a protective effect on fracture (OR = 0.67, 95% CI: 0.54 to 0.84; $P = 4.42 \times 10^{-4}$; P-adjusted = 3.53×10^{-3}). The causal effect estimate was consistent from different MR methods. It was 0.69 (95% CI: 0.52 to 0.92; $P = 0.013$) in weighted median, 0.67 (95% CI: 0.54 to 0.84; $P = 4.42 \times 10^{-4}$) in MR-Lasso, 0.67 (95% CI: 0.56 to 0.81; $P = 3.33 \times 10^{-5}$) in MR-Robust, 0.67 (95% CI: 0.51 to 0.86; $P = 0.002$) in MR-RAPS, and 0.67 (95% CI: 0.55 to 0.82; $P = 0.028$) in MR-PRESSO. Genetically predicted CCBs were associated with higher fracture risk (OR = 1.07, 95% CI: 1.03 to 1.12; $P = 0.002$; P-adjusted = 0.013). Again, the results are consistent across different MR methods, including weighted median method (OR = 1.09, 95% CI: 1.01 to 1.17; $P = 0.019$), MR-Lasso (OR = 1.08, 95% CI: 1.04 to 1.13; $P = 2.56 \times 10^{-4}$), MR-Robust (OR = 1.08, 95% CI: 1.04 to 1.13; $P = 3.59 \times 10^{-4}$), MR-RAPS (OR = 1.08, 95% CI: 1.03 to 1.14; $P = 0.001$), and MR-PRESSO (OR = 1.07, 95% CI: 1.03 to 1.12; $P = 0.003$). In addition, further analysis suggested that no horizontal pleiotropy (Egger intercept $P = 0.137$ for ARBs and 0.157 for CCBs) and no heterogeneity (Cochran'Q test $P = 0.947$ for ARBs and 0.289
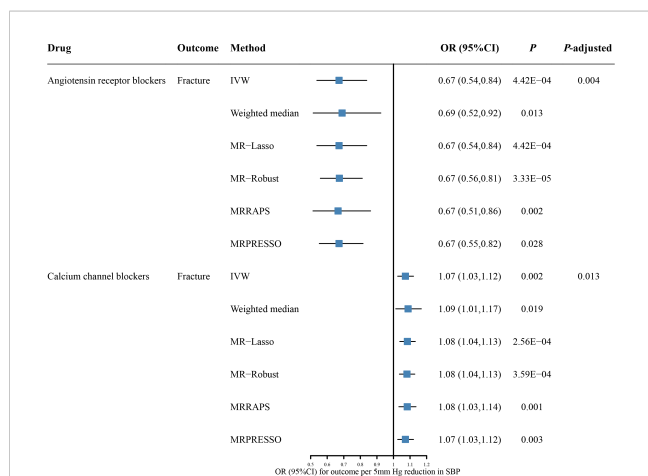
for CCBs) (Supplementary Table 3). The LOO plots showed no distortion, indicating that no single SNP can have a substantial impact on the results (Supplementary Figure 2).

3.3 Drug-target MR analysis for TB-BMD and eBMD

The drug-target MR analysis was also performed to assess the causal effects of antihypertensive drugs on TB-BMD and eBMD (Figure 3; Supplementary Tables 5, 6). We identified significant causal associations of genetically predicted ARBs with higher TB-BMD (β = 0.36, 95% CI: 0.11 to 0.61; $P = 0.005$; P-adjusted = 0.022) (Supplementary Table 5). The results remained consistent across the weighted median (β = 0.36, 95% CI: 0.04 to 0.68; $P = 0.027$), MR-Lasso (β = 0.36, 95% CI: 0.11 to 0.61; $P = 0.005$), MR-Robust (β = 0.36, 95% CI: 0.20 to 0.52; $P = 1.06 \times 10^{-5}$), and MR-RAPS (β = 0.36, 95% CI: 0.06 to 0.66; $P = 0.017$). We also found associations between genetically predicted PSDs with higher TB-BMD (β = -0.61, 95% CI: -0.88 to -0.33; $P = 0.039$; P-adjusted = 1.86×10^{-4}). However, the causal association should be interpreted cautiously given with only two SNPs for PSDs. There was no pleiotropy detected from MR-Egger regression model (MR-Egger intercept $P = 0.514$ for ARBs) or Cochran's Q test ($P = 0.880$ for ARBs and 0.926 for PSDs) (Supplementary Table 3). The LOO analyses also showed no outlier SNPs (Supplementary Figure 3). In addition, genetic proxies for thiazide diuretics were positively associated with TB-BMD at a nominal threshold (β = 0.24, 95% CI: 0.01 to 0.47; $P = 0.039$; P-adjusted = 0.134) (Supplementary Table 5).

In a further assessment of antihypertensive drugs in eBMD, genetic proxies for ARBs and thiazide diuretics were associated with

FIGURE 2
The causal effects of genetic proxies for antihypertensive drug classes on risk of fracture. CI, confidence interval; OR, odds ratio; SBP, systolic blood pressure; IVW, inverse-variance weighted; MR, Mendelian randomization; MR-RAPS, Robust Adjusted Profile Score; MR-PRESSO, Mendelian randomization Pleiotropy RESidual Sum and Outlier.

FIGURE 3
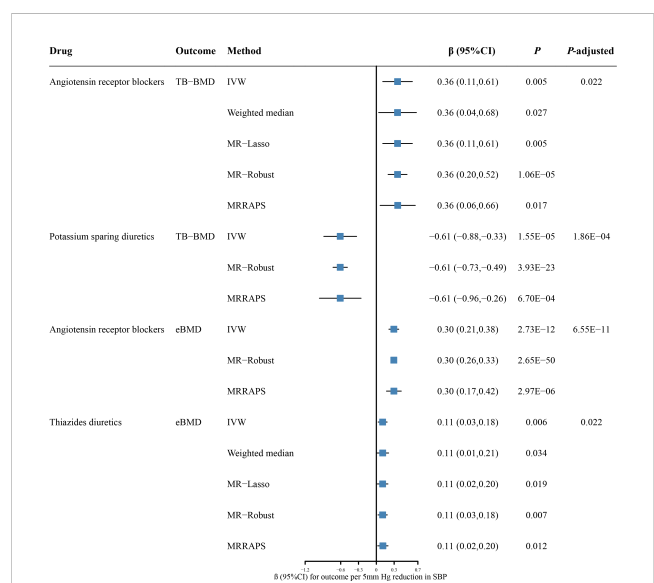The causal effects of genetic proxies for antihypertensive drug classes on BMD. CI, confidence interval; TB-BMD, total body bone mineral density; eBMD, estimated heel bone mineral density; SBP, systolic blood pressure; IVW, inverse-variance weighted; MR, Mendelian randomization; MR-RAPS, Robust Adjusted Profile Score; MR-PRESSO, Mendelian randomization Pleiotropy RESidual Sum and Outlier.

higher eBMD (β = 0.30, 95% CI: 0.21 to 0.38; $P = 2.73 \times 10^{-12}$; P-adjusted = 6.55×10^{-11} for ARBs; β = 0.11, 95% CI: 0.03 to 0.18; $P = 0.006$; P-adjusted = 0.022 for thiazide diuretics) (Figure 3; Supplementary Table 6). The causal effect estimates remained from the weighted median, MR-Lasso, MR-Robust, and MR-RAPS methods (Figure 3). Our analysis suggested no significant evidence of horizontal pleiotropy (Egger intercept $P = 0.822$ for thiazide diuretics). Furthermore, there was no statistically significant heterogeneity between antihypertensive drugs and eBMD (Cochran'Q test $P = 0.646$ for ARBs and 0.247 for thiazide diuretics) (Supplementary Table 3). The LOO analyses also showed no outlier SNPs (Supplementary Figure 4). There was no evidence of causal association for other antihypertensive drugs on eBMD (Supplementary Table 6).

3.4 Sensitivity analysis

There were six potentially pleiotropic SNPs identified by Phenoscanner (Supplementary Table 7), and after removing these SNPs, the results were consistent with previously significant associations (Supplementary Table 8, 9).

4 Discussion

A comprehensive drug target MR analysis was conducted to infer potential causal effects for antihypertensive drugs on fracture and BMD, with the schematic of the significant findings provided in Figure 4. The results showed that the genetic proxies for ARBs were associated with lower fracture risk, higher TB-BMD, and higher eBMD. Meanwhile, genetically predicted CCBs were associated with higher fracture risk. Genetic proxies for thiazide diuretics had positive associations with eBMD, while genetic proxies for PSDs showed negative associations with TB-BMD. More importantly, the results were verified by multiple MR methods, which suggested reliability and consistency.

Previous studies illustrated that ARBs use was associated with lower fracture risk compared to non-users. The study of the Women's Health Initiative found that long-term ARBs use was associated with a reduced risk of all fractures in postmenopausal women (34). Another cohort study revealed a reduced risk of hip fracture in people with ARBs medications (35). Angiotensin II

receptor blockers imposed their pharmacological effects by affecting the renin aldosterone angiotensin system (RAAS). In addition to acting systemically, RAAS played a role locally in bone tissue (36). Osteoblasts and osteoclasts have been discovered to express angiotensin II, indicating the presence of local RAAS in bone (37). RAAS might adjust bone metabolism via affecting the RANKL/RANK/OPG system (38). Thus, several animal studies have demonstrated the prevention of osteoporosis by blocking the angiotensin II pathway (39), increasing bone mass and strength (37) as well as accelerating bone healing and remodeling (40). Notably, consistent with previous cohort studies (41), we did not find that ACEIs (another RAAS inhibitor) were significantly associated with fracture risk or BMD. A recent meta-analysis also indicated that ACEIs use was not significantly associated with fracture risk, while ARBs use was associated with a lower risk of fracture (42). The mechanisms underlying the differences in the effects of the two RAAS inhibitors remain to be further investigated.

Previous researches on the relationships between CCBs and fracture risk and BMD were inconclusive. A Danish case-control study found a 6% reduction in fracture risk with CCBs use (43), while another study found an association between CCBs use and increased fracture risk (44). A large cohort study illustrated that there was no significant association between CCBs use and hip fracture risk (41). CCBs may affect bone metabolism, as they act by interfering with the transport of calcium through the cell membrane (45). Altering the activity of L-type calcium channels through drugs may modulate growth and differentiation of osteoblasts and stimulates the function of these cells (46). Some animal studies have suggested that CCBs may interfere with the production of steroid hormones and affect the process of bone repair and remodeling (47, 48), which may partly explain our results. However, some other studies pointed out that such agents may lead to reduced bone resorption and formation by directly or indirectly inhibiting the function and activity of osteoclasts (49, 50). Further mechanism studies were required to clarify the effects of CCBs on bone metabolism.

Thiazide diuretics, as one of the most common antihypertensive drugs, were generally considered to have a beneficial effect on BMD (51). Several RCTs indicated that thiazide diuretics could increase BMD in people with a high risk of osteoporosis compared to placebo (52, 53). Thiazide diuretics slowed bone loss by reducing urinary calcium excretion and stimulated osteoblast differentiation and bone mineral formation (54). Although many observational
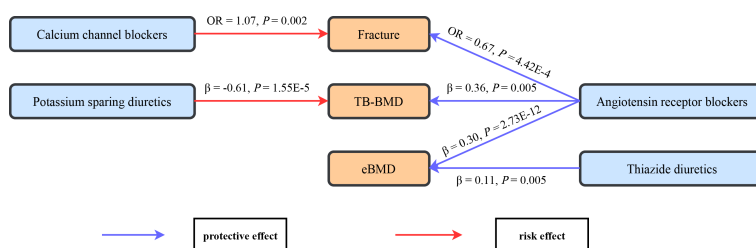

FIGURE 4
The schematic for the significant causal effects of antihypertensive drugs on bone health-related traits. Significant causal effects are presented as arrows with the estimated effect sizes alongside, with the red arrow representing risk effect and the blue arrow representing protective effects. TB-BMD, total body bone mineral density; eBMD, estimated heel bone mineral density.

studies have assessed the potential associations between the use of thiazide diuretics and fracture risk, the findings remain to be inconsistent. An updated meta-analysis concluded that thiazide diuretics use was not a protective factor for fracture, given that thiazide diuretics were associated with a lower fracture risk only in case-control studies, rather than cohort studies (55). The metabolic alkalosis (56), hyponatremia (57), and upright hypotension (58) resulting from the use of thiazide diuretics may counteract their beneficial effects on calcium homeostasis and BMD, which may result in thiazide diuretics having little effect on the risk of osteoporotic fracture (59). Overall, thiazide diuretics could have a positive effect on BMD, although this effect is not always correlated with a decreased risk of fracture.

This study has several strengths. First, it used genetic variants mimicking antihypertensive drugs to examine the effect of drugs by drug target MR. This approach overcome limitations for observational studies, including reverse causality and potential confounders, while avoiding the time and resource constraints of RCTs. Second, the study utilized GWAS data sourced from the largest genetic studies to date, enhancing the statistical validity of the findings and conclusions. Third, genetic variants in the drug target genes associated with systolic blood pressure were first screened as proxies for antihypertensive drugs through strict selection procedures, followed by positive control analysis to ensure the validity of the genetic instruments. Fourth, various sensitivity analyses were conducted to validate reliability and consistency.

Our study is not without limitations. First, drug-target MR analysis evaluates long-term drug effects, which may have greater effect values than short-term drug effects in clinical trials. Therefore, this study may be more meaningful in providing direction for causal associations of drugs. Second, potential horizontal pleiotropy may affect the drug effects of MR analysis. We used instrumental variables near the genes encoding the drug targets, which minimized the possibility of pleiotropy. Also, there was no evidence of pleiotropy using several sensitivity analysis methods. Third, the association of genetically proxied ACEIs and CAD in positive control is not significant, which was similar to other MR studies (60, 61). This may indicate that the effect of ACEIs on CAD may be mediated through other pathways, not just the ACE target. Finally, our study data were confined to populations of European origin to ascertain genetic homogeneity. Hence, additional investigations and verification are warranted when the results are extrapolated to other ethnic groups with distinct genetic profiles.

5 Conclusion

The present study provided evidence for causal associations of antihypertensive drugs with fracture risk and BMD. These findings suggest that genetic proxies for ARBs and thiazide diuretics may have a protective effect on bone health, while genetic proxies for CCBs and PSDs may have a negative effect. This study supports the repurposing of antihypertensive drugs in the field of bone health and helps develop beneficial hypertension drug regimens for people with poor bone health in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

ZY and MZ participated in conceiving and designing the study. XH and TZ completed the statistical analysis and drafted the manuscript. PG, WG, and HZ provided valuable advice during the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1164387/full#supplementary-material

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