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**Original Article**

# Associations between Atrial Fibrillation and Bone Mineral Density at Different Sites: A Mendelian Randomization Study

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**Abstract:**

**Background:** Observational studies have suggested that anti-osteoporosis therapies may increase the risk of atrial fibrillation (AF); however, whether bone mineral density (BMD) itself exerts a causal effect on AF remains unclear. This study systematically investigated the univariable causal relationship between AF and BMD at different skeletal sites, including the femoral neck, lumbar spine, forearm, and total body, to clarify the relationship between bone status and AF risk.

**Methods:** We conducted a two-sample univariable Mendelian randomization (MR) analysis to evaluate the causal associations between AF and BMD measured at the femoral neck (FN-BMD), lumbar spine (LS-BMD), forearm (FA-BMD), and total body (TB-BMD). Summary statistics were obtained from large-scale genome-wide association studies (GWASs). The inverse variance-weighted (IVW) method was used as the primary method, with sensitivity analyses including Cochran's Q test, the MR-Egger intercept test, and leave-one-out analyses.

**Results:** The IVW analysis indicated positive associations of FN-BMD (odds ratio [OR] = 1.17, 95% confidence interval [CI]: 1.05–1.29, $P$ = 0.003) and FA-BMD (OR = 1.15, 95% CI: 1.03–1.29, P = 0.01) with an increased AF risk. In contrast, lumbar spine bone mineral density (LS-BMD) had a suggestive causal association with AF(OR = 1.12, 95% CI: 1.02-1.23, P = 0.014).In contrast, no significant associations were detected for TB-BMD (OR = 1.02, 95% CI: 0.95–1.09, $P$ = 0.64). Sensitivity analyses supported the robustness of these findings.

**Conclusion:** This MR study provides genetic evidence that increased FN-BMD and FA-BMD is causally associated with an increased risk of AF, whereas lumbar spine bone mineral density (LS-BMD) exerted a suggestive causal effect, whereas total-body bone mineral density (TB-BMD) showed no significant causal effect.. These results highlight novel links between skeletal health and cardiovascular disease.

**Keywords: Mendelian randomization, atrial fibrillation, bone mineral density, causality**

## Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia and is associated with a higher risk for ischemic stroke, heart failure, and mortality, thereby affecting quality of life and prognosis of patients[1]. In the United States, the prevalence of AF is projected to increase from 2.2 million people in 2010 to 6–12 million people by 2050, due to increased life expectancy and improved survival among patients with cardiovascular conditions[2]. I In Europe, 17.9 million people are expected to be affected by AF[2]. Over the past decade, the incidence and multimorbidity of AF have consistently depicted an escalating trend globally[3]. Therefore, AF has garnered increasing attention, with early prevention and intervention being critical research points. Currently, the etiology of AF is unclear, underscoring the need to explore AF pathogenesis.

Osteoporosis (OP) is another major public health concerns in the United States and worldwide[4]. Although the number of people diagnosed with OP is similar to that for cardiovascular disease and dementia, OP is often easily overlooked[5]. This condition is characterized by decreased bone mineral density (BMD) and is a chronic age-related disease that is primarily diagnosed using dual-energy X-ray absorptiometry (DXA)[6]. The relationship between BMD and cardiovascular disease has been reported, as the two conditions share common risk factors. Previous studies have shown that a decrease in cardiovascular disease incidence is associated with an increase in BMD among female populations in the United States [7]. The central nervous system plays an important regulatory role in bone metabolism [8]. Both human and animal experiments have indicated that sympathoinhibitory drugs, such as beta-blockers, can alter bone turnover, thereby increasing BMD and reducing fracture risk [9-11]. Power spectral analysis of heart rate variability (HRV) can non-invasively detect the activity level of the body's autonomic nervous system [12]. Previous studies have demonstrated that reduced HRV is associated with lower BMD and an elevated risk of fractures in patients with type 2 diabetes mellitus. Furthermore, cardiovascular autonomic neuropathy in patients with type 2 diabetes mellitus is associated with reduced BMD and increased fracture risk, whereas the low-frequency/high-frequency ratio of HRV has been proposed as a predictive marker for diabetic OP[13]. These findings indicate a correlation between HRV and BMD; nonetheless, there has been limited research on the relationship between BMD and AF. Therefore, exploring the causal relationship between AF and BMD is crucial.

Mendelian randomization (MR) is a widely employed epidemiological approach that uses genetic variants as instrumental variables (IVs) to infer causal effects of exposures on outcomes[14]. Because genetic variants are randomly allocated at conception, MR minimizes the influence of reverse causation and residual confounding, provided that its core assumptions are satisfied. Consequently, MR has become a powerful tool for strengthening causal inference in situations where randomized controlled trials are impractical or unethical. To date, no comprehensive MR study has systematically evaluated the causal relationship between BMD at multiple skeletal sites and AF. Leveraging publicly available genome-wide association study (GWAS) summary statistics, the present study investigated the univariable causal associations between AF and BMD measured at the femoral neck, lumbar spine, forearm, and total body.

Accordingly, we performed a two-sample univariable MR analysis using large-scale GWAS datasets to determine whether genetically predicted BMD influences AF risk.

## 2. Materials and methods

### 2.1 Study design

The basic principles of the MR study design are as follows: IVs are independent of confounding factors but correlated with exposure factors, and they have no direct association with outcome variables and can only exert indirect effects on outcomes via exposure factors. This method is suitable for investigating long-term exposures and clinical outcomes with delayed onset, avoiding biases induced by reverse causation and residual confounding. In this study, AF was set as the outcome variable, BMD (total body and multiple skeletal sites) served as the exposure factor. Genetic loci associated with BMD from corresponding GWASs were selected as IVs. A two-sample MR design was adopted to explore the causal association between BMD and AF. In clinical practice, because dual-energy X-ray absorptiometry (DXA) is the gold standard for OP diagnosis and evaluates the lumbar spine, forearm, and femoral neck [15]. , BMD measured at these four skeletal sites was included in the

analysis: femoral neck (FN-BMD), lumbar spine (LS-BMD), forearm (FA-BMD), and total body (TB-BMD), serving as exposure variables, whereas AF was the outcome variable. For this analysis, IVs were single nucleotide polymorphisms (SNPs), chosen based on three key assumptions: (1) exposure variables must exhibit a consistent correlation with the genetic IV; (2) when used as IVs, genetic variations should not be associated with confounding factors; and (3) the genetic IV should influence the outcome only through the exposure, and not by any other means[16] . All participants in the initial GWASs provided informed consent, with approval granted by the relevant institutional review committees. The experimental design is depicted in Figure 1.

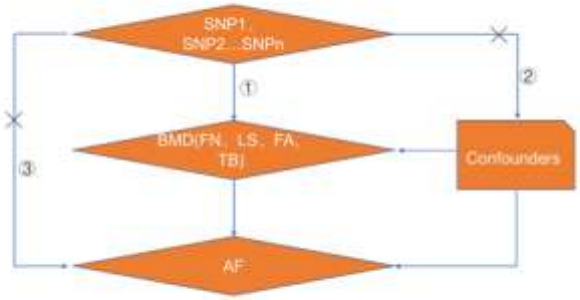


**Figure 1 Study design for Mendelian randomization analysis.**

2.2 GWAS Summary Data

Summary-level GWAS statistics for FN-BMD, LS-BMD, and FA-BMD were obtained from meta-analyses conducted by the Genetic Factors for Osteoporosis (GEFOS) Consortium. These datasets included 32,735 individuals for FN-BMD, 28,498 for LS-BMD, and 8,143 for FA-BMD. Summary statistics for TB-BMD, comprising 56,284 participants, were obtained from an independent large-scale GWAS meta-analysis. All datasets were accessed through the GWAS Open Database (https://gwas.mrcieu.ac.uk/; accessed in March 2024). The TB-BMD dataset was derived from the EBI GWAS Catalog (ebi-a-GCST005348; 2018), a well-established life-course GWAS meta-analysis characterized by standardized phenotype definitions and rigorous cross-cohort quality-control procedures, thereby ensuring reliable genetic effect estimates and consistency with previous bone genetics studies. The LS-BMD (28,498 individuals; 10,582,897 SNPs) and FN-BMD (32,735 individuals; 9,955,366 SNPs) datasets were obtained from validated IEU GWAS resources (ieu-a-982 and ieu-a-980, respectively). Distal forearm BMD data were extracted from the authoritative IEU dataset (ieu-a-977), which included 8,143 individuals of European ancestry and 10,448,071 SNPs. To our knowledge, no updated public GWAS dataset for this specific skeletal phenotype is currently available. As of May 2024, the Medical Research Council (MRC) Integrative Epidemiology Unit (IEU) at the University of Bristol hosted 50,044 publicly accessible GWAS datasets. Summary statistics for AF were obtained from the FinnGen R10 GWAS dataset (GWAS ID: finngen_R10_I9_AF), which included 50,743 cases and 210,652 controls of European ancestry. The FinnGen project represents a large population-based genomic resource that

capitalizes on the relative genetic homogeneity of the Finnish population to facilitate the identification of disease-associated genetic variants [17]. Uniform and strict screeningTo maximize data quality and minimize potential bias, datasets were selected according to four predefined criteria. All participants were restricted to individuals of European ancestry to reduce population stratification. Only GWAS datasets with clearly defined phenotypes, standardized measurement protocols, and robust quality-control procedures were included. Exposure and outcome datasets were required to be independent to minimize bias arising from sample overlap. Finally, only studies that assessed BMD using standardized DXA measurements were selected to ensure consistency across skeletal phenotypes. Detailed information for each GWAS dataset is summarized in Table 1.

**Table 1 Detailed information of studies and datasets used for Mendelian randomization analyses.**

| Phenotype | GWAS ID | Data source | Sample size | Population |
|---|---|---|---|---|
| FN-BMD | ieu-a-980 | GEFOS consortium | 32,735 | European |
| LS-BMD | ieu-a-982 | GEFOS consortium | 28,498 | European |
| FA-BMD | ieu-a-977 | GEFOS consortium | 8,143 | European |
| TB-BMD | ebi-a-GCST005348 | Medina-Gomez C | 56,284 | European |
| AF | finngen_R10_I9_AF | FinnGen consortium | 261,395 | European |

FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar spine bone mineral density; FA-BMD, forearm bone mineral density; TB-BMD, total bone mineral density; AF, Atrial fibrillation; GEFOS, Genetic Factors for Osteoporosis.

### 2.3 Selection of Genetic Instruments

To ensure that there is no linkage imbalance (LD) between SNPs that affects the analysis results, we chose LD clustering with R2<0.001 and a minimum window size of 10000 kb. To reduce weak instrument bias, as mentioned earlier, the strength of each SNP was calculated using F-statistics, which was explained by considering the exposure differences ($R^2$) explained by the SNPs in each exposure using the formula $[(N - K - 1) / K \times R^2 / (1 - R^2)]$, where K represents the number of SNPs and N represents the sample size [18]. SNPs with an F-statistic F < 10 were considered weak IVs and were excluded from subsequent MR analyses. Finally, the MR-PRESSO method was used to detect outliers; SNPs identified as outliers were removed, and the remaining SNPs were analyzed.

### 2.4 Statistical analysis

Five complementary MR methods were used to estimate the causal association between BMD and AF, including inverse variance-weighted (IVW), weighted median, MR-Egger regression, weighted mode, and simple mode analyses. The IVW method was designated as the primary analytical approach because it provides the greatest statistical efficiency when all IVs are valid or when horizontal pleiotropy is absent. Effect estimates are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs), representing the change in AF risk per one standard deviation increase in genetically predicted BMD [19]. Because four independent BMD phenotypes (FN-BMD, LS-BMD, FA-BMD, and TB-BMD) were evaluated, Bonferroni correction was applied to account for multiple

comparisons, resulting in a statistical significance threshold of $P < 0.0125$ (0.05/4). Several complementary sensitivity analyses were performed to assess the robustness and validity of the MR findings. MR-PRESSO was used to identify and remove outlier SNPs with potential pleiotropic effects. Cochran's Q test was applied to evaluate heterogeneity among IVs, with $P < 0.05$ indicating significant heterogeneity. Leave-one-out analysis was conducted to determine whether the overall causal estimate was disproportionately influenced by any individual SNP. In addition, MR-Egger regression and the weighted median method were used to examine the consistency of the causal estimates and evaluate the presence of directional horizontal pleiotropy. Funnel plots and forest plots were generated to visualize the distribution of SNP-specific estimates and further assess the robustness of the findings. All statistical analyses were performed using R software (version 4.3.3) with the TwoSampleMR and MR-PRESSO packages.

## 3. Results

We performed an MR analysis to investigate the causal effects of BMD at different skeletal sites on AF risk. Prior to the MR analyses, exposure and outcome datasets were harmonized to ensure consistent alignment of effect alleles. Following the predefined quality-control criteria, 20 SNPs were initially selected as IVs for FN-BMD, 24 for LS-BMD, 3 for FA-BMD, and 82 for TB-BMD. After MR-PRESSO analysis, two outlying SNPs (rs71390846 and rs894738) were excluded from the LS-BMD analysis, and three outlying SNPs (rs71390846, rs7209460, and rs9478217) were excluded from the FN-BMD analysis; in the TB-BMD analysis, three SNPs (rs71390846, rs6557155, and rs2873195) were removed. Table 2 reports the final corrected estimates after MR-PRESSO outlier removal.Both the individual IV F-statistics and the overall F-statistics exceeded 10, suggesting that weak instrument variation was unlikely to influence the results.

**Table 2 Complementary analyses of the associations of genetically predicted different sites of bone mineral density with Atrial fibrillation**.

| Exposures | Outcome | SNPs,n | Method | β (95%CI) | P value |
|---|---|---|---|---|---|
| FN-BMD | AF | 17 | MR Egger | -0.03(-0.52, 0.46) | 0.912 |
| | | 17 | Weighted median | 0.18(0.05,0.31) | 0.004 |
| | | 17 | Inverse variance weighted | 0.15(0.05,0.25) | 0.003 |
| | | 17 | Simple mode | 0.23(0.00,0.45) | 0.069 |
| | | 17 | Weighted mode | 0.24(0.02,0.47) | 0.040 |
| LS-BMD | AF | 22 | MR Egger | 0.01(-0.33,0.34) | 0.950 |
| | | 22 | Weighted median | 0.06(-0.04,0.15) | 0.240 |
| | | 22 | Inverse variance weighted | 0.12(0.02,0.21) | 0.014 |
| | | 22 | Simple mode | 0.07(-0.09,0.22) | 0.404 |
| | | 22 | Weighted mode | 0.05(-0.08,0.19) | 0.453 |
| FA-BMD | AF | 3 | MR Egger | 0.06(-0.37,0.49) | 0.826 |
| | | 3 | Weighted median | 0.12(0.02,0.23) | 0.024 |
| | | 3 | Inverse variance weighted | 0.14(0.03,0.25) | 0.011 |
| | | 3 | Simple mode | 0.10(-0.05,0.25) | 0.324 |
| | | 3 | Weighted mode | 0.12(-0.00,0.24) | 0.190 |
| TB-BMD | AF | 79 | MR Egger | -0.01(0.19,0.17) | 0.918 |

| | | | | | |
|---|---|---|---|---|---|
| | | 79 | Weighted median | 0.06(-0.02,0.13) | 0.130 |
| | | 79 | Inverse variance weighted | 0.02(-0.05,0.08) | 0.639 |
| | | 79 | Simple mode | 0.06(-0.09,0.21) | 0.453 |
| | | 79 | Weighted mode | 0.08(-0.02,0.19) | 0.128 |

FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar spine bone mineral density; FA-BMD, forearm bone mineral density; TB-BMD, total bone mineral density; AF, Atrial fibrillation; MR, Mendelian randomization; SNP, single-nucleotide polymorphism; CI, confidence interval.

The primary causal estimates were generated using the IVW method, which demonstrated a significant positive association between genetically predicted FN-BMD and AF risk (OR = 1.19, 95% CI = 1.02–1.38, $P < 0.05$). MR-PRESSO identified three outlying SNPs (rs71390846, rs7209460, and rs9478217); however, removal of these outliers did not materially alter the observed causal association, indicating that the findings were robust. A significant positive association was also observed between FA-BMD and AF (OR = 1.15, 95% CI = 1.03–1.29, $P < 0.05$). Because only three instrumental SNPs were available for FA-BMD, the MR-PRESSO global test could not be performed for this analysis. A significant association was likewise detected between LS-BMD and AF in the primary IVW analysis (OR = 1.07, 95% CI = 1.00–1.15, $P >0.05$). Nevertheless, MR-PRESSO identified two outlying SNPs (rs71390846 and rs894738), and the association was no longer statistically significant after these variants were excluded (OR = 1.13, 95% CI = 1.02–1.24, $P <0.05$), its $P$ value was 0.014, marginally higher than the corrected threshold of 0.0125, yet this result indicated a suggestive causal association.. In contrast, no significant causal association was observed between TB-BMD and AF (OR = 1.02, 95% CI = 0.95–1.09, $P > 0.05$). MR-PRESSO detected three outliers (rs71390846, rs6557155, and rs2873195) in the TB-BMD analysis, and exclusion of these variants did not change the null association ($P > 0.05$). MR-Egger analysis did not suggest any directional pleiotropy for the IVs (P for intercept = 0.468 for FN-BMD, 1.000 for LS-BMD, 0.767 for FA-BMD, and 0.602 for TB-BMD). Together with the MR-PRESSO global test, these results indicate that the MR analysis was still robust and was unaffected by any potential level of pleiotropy ($P > 0.05$). Funnel plots were employed to assess potential asymmetry, which may indicate the presence of directional level pleiotropy (Figure 2). In addition, the LOO analysis did not reveal any influence of high-impact SNPs on the estimation of summary effects (Figure 3). Finally, the forest plots illustrated the effects of each SNP on the outcome, and no outliers were found (Figure 4). Scatter plots further illustrated the potential causal relationships between BMD at different skeletal sites and AF risk (Figure 5), with upward slopes indicating positive causal effects and downward slopes indicating negative causal effects.

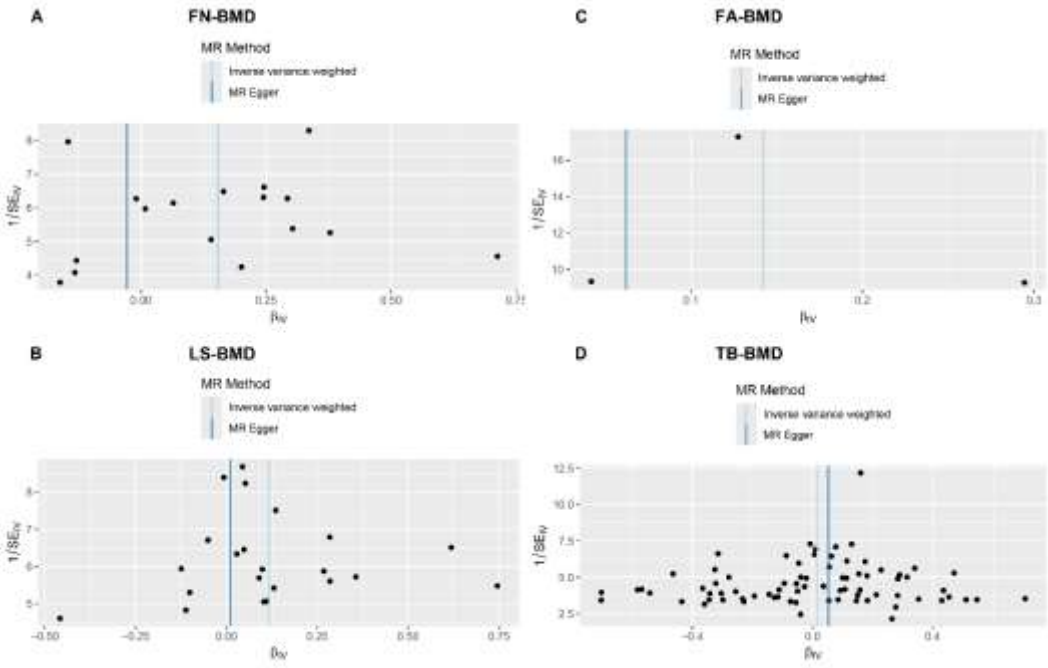


**Figure 2 MR funnel plots for relationship of different sites of bone mineral density on Atrial fibrillation.(A), Funnel plot of SNPs effects FN-BMD vs AF; (B), Funnel plot of SNPs effects on LS-BMD vs AF; (C), Funnel plot of SNPs effects on FA-BMD vs AF; (D), Funnel plots of SNPs effects on TB-BMD vs AF.**

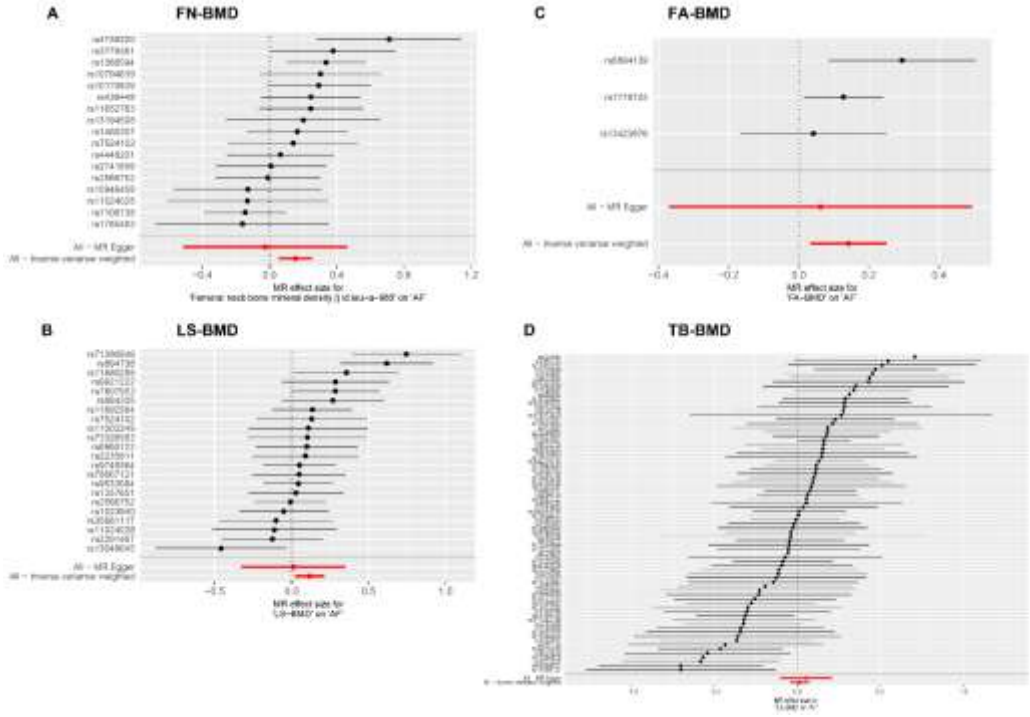


**Figure 3 MR leave-one-out plots for relationship of different sites of bone mineral density on Atrial fibrillation. (A), Leave-one-out plot of SNPs effects FN-BMD vs AF; (B), Leave-one-out plot of SNPs effects on LS-BMD vs AF; (C), Leave-one-out plot of SNPs effects on FA-BMD vs AF; (D), Leave-one-out plot of SNPs effects on TB-BMD vs AF.**

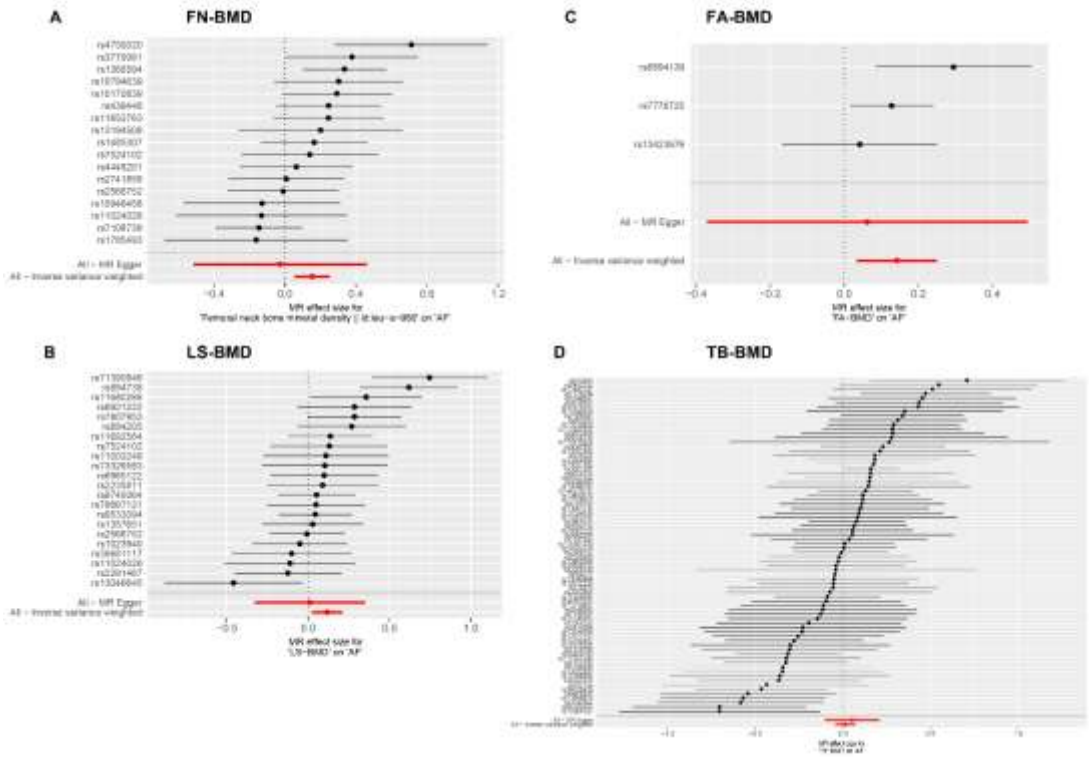


**Figure 4 MR forest plots for relationship of different sites of bone mineral density on Atrial fibrillation. .(A), Forest plot of SNPs effects FN-BMD vs AF; (B), Forest plot of SNPs effects on LS-BMD vs AF; (C), Forest plot of SNPs effects on FA-BMD vs AF; (D), Forest plots of SNPs effects on TB-BMD vs AF.**

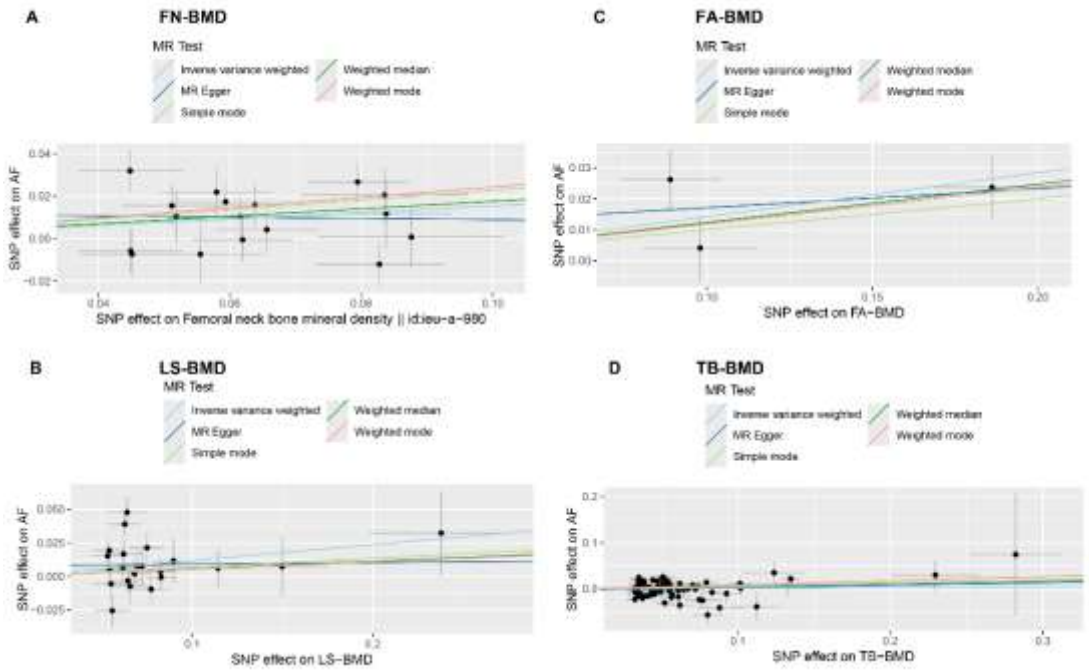


**Figure 5 MR scatter plots for relationship of different sites of bone mineral density on Atrial fibrillation. .(A), Scatter plot of SNPs effects FN-BMD vs AF; (B), Scatter plot of SNPs effects on LS-BMD vs AF; (C), Scatter plot of SNPs effects on FA-BMD vs AF; (D), Scatter plots of SNPs effects on TB-BMD vs AF.**

## Discussion

Although advanced age and female sex are associated with an increased risk of AF, the absolute incidence rate seems to be higher in men, suggesting that other risk factors have different effects on both sexes[20]. As opposed to the traditional view that bone is an inert organ primarily responsible for body protection and locomotion, increasing evidence has proposed that bone is an endocrine organ capable of regulating multiple organs and tissues via the secretion of bone-derived signaling hormones[21]. Bones are active endocrine organs that carry out several metabolic functions. Thyroid hormones regulate bone remodeling by modulating osteoclast generation and activity [22] and have a significant impact on cardiac function and structure, making them susceptible to diseases such as AF and heart failure. Excessive levothyroxine supplementation has been associated with harmful and pathological effects, such as arrhythmia (most commonly AF) and OP[23]. In addition, diabetes increases the risk of both AF and reduced BMD [24,25] . Furthermore, vitamin D insufficiency or deficiency has been associated with an increased risk of AF in the general population, although further research is warranted to determine the role of vitamin D supplementation in preventing AF[26]. Despite the well-established role of vitamin D in bone metabolism, findings from intervention trials in patients at risk of cardiovascular disease or diagnosed with cardiovascular disease are conflicting[27]. Therefore, exploring the causal relationship between BMD and AF is particularly important.

Atrial remodeling is considered the pathological basis for AF development and maintenance. A key regulatory system in bone metabolism is the osteoprotegerin (OPG)/nuclear factor kappa B receptor activator (RANK)/RANK ligand (RANKL) signaling axis, which has a potential role in the pathogenesis of AF and may become a new target for therapeutic interventions[28]. RANKL regulates osteoblast/osteoclast activity and plays an important role in OP treatment [29,30]. In addition, the Wnt/β-catenin signaling pathway is also involved in AF development [31] and OP [32]. Inflammation, immune cells, macrophages, and others have also been reported to contribute to atrial remodeling in AF patients[33], , and similar inflammatory mechanisms also contribute to OP. These findings indicate a causal relationship between BMD and AF.

Early reports raised concerns that bisphosphonate therapy might increase AF incidence. Subsequent studies, however, found only a weak correlation between intravenous bisphosphate infusion and QTc interval prolongation, without sufficient evidence to explain the association between intravenous bisphosphate infusion and any changes in electrocardiogram variables that may cause AF [34]. More recently, romosozumab has been indicated as a new treatment for OP in postmenopausal women. However, post-marketing surveillance indicated a potential increase in AF risk after romosozumab treatment[35]. In addition, zoledronic acid has been reported to increase AF risk and arrhythmia compared with placebo in women with primary OP[36]. These observations raise the possibility that pharmacologic interventions for OP may increase the incidence of AF. While the occurrence of AF may be caused by exposure to newly introduced OP therapies, this association may reflect underlying pathophysiological links between BMD and AF development. Long-term warfarin use as AF treatment has been associated with an increased risk of osteoporotic fractures in male patients[37]. In contrast, direct oral anticoagulants, especially apixaban, can relatively reduce fracture risk[38]. These observations further support an association between AF therapies and increased OP risk. Although the HUNT study from Norway found no association between distal forearm BMD and AF[39], the results may be biased due to

limitations such as the population. Moreover, this study evaluated the risk of cardiovascular disease using BMD as a risk factor, which may lead to further bias in the experimental results and neglect the positive correlation between BMD and AF. Consequently, the relationship between BMD and cardiovascular disease remains controversial[40].

Our MR analysis provides genetic evidence supporting previous observations that low regional BMD correlates with higher arrhythmia susceptibility; moreover, genetically reduced FN-BMD and FA-BMD were causally associated with increased AF risk, whereas no causal associations were found for TB-BMD or LS-BMD. Such site-specific heterogeneity may explain the inconsistent findings reported in prior studies, many of which commonly adopted generalized BMD measurements without considering regional skeletal differences. The absence of casual associations suggest that previously reported epidemiological correlation between generalized bone loss and AF may reflect residual confounding or reverse causation.

Unlike previous investigations that primarily examined the effects of AF on bone deterioration, our study evaluated the reverse causal pathway. By eliminating conventional biases, our findings refine current evidence by suggesting that reduced regional (femoral neck and forearm) BMD, instead of whole-body or lumbar BMD, serves as an independent genetic risk factor for AF, providing a precise therapeutic target for AF prevention in OP patients.

Our analyses demonstrate a genetic causal relationship between FN-BMD and FA-BMD with AF, while there is a suggestive genetic causal relationship between LS-BMD and AF.In contrast, no causal relationship was noted for TB-BMD , which indirectly indicates that increasing TB-BMD does not increase AF incidence. These findings suggest that excessively rapid improvement in BMD during pharmacological treatment of OP may not be advisable in clinical practice, as rapid increases in FN-BMD and FA-BMD may lead to an increased incidence of AF.

Our research has some limitations. First, the GWAS datasets were derived predominantly from the European population, which may limit the generalizability of our findings to other populations. Second, the limited exposure variance explained by the selected SNPs may lead to weak IV bias; therefore, larger GWAS datasets are needed to enhance the ability of related MR studies to detect associations. Conventional randomized controlled trials face challenges in effectively exploring these causal relationships due to their high cost and long duration. Although the present findings provide evidence supporting a causal association between BMD and AF, this relationship has not yet been fully established. A more comprehensive understanding of the causal relationship between these conditions would facilitate strategies to prevent potential adverse consequences. The application of genetic variation in investigating causality can effectively circumvent confounding, thereby strengthening causal inference[41]. Nevertheless, further validation is warranted through studies using individual-level data, multicenter observational cohorts, and large-scale randomized controlled trials to validate the robustness of these findings.

**Conclusions**

In summary, our MR study demonstrated that FN-BMD and FA-BMD are associated with the risk of AF, whereas LS-BMD showed a suggestive genetic causal association with AF, while no causal relationship was observed for TB-BMD. . These findings suggest that targeting these factors may provide a promising strategy for AF prediction in patients with OP.

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CRediT authorship contribution statement

XL: Validation, Formal analysis, Writing – original draft. JC: Project administration, Supervision, Validation, Formal analysis. Writing – review &editing XZ: Data curation, Conceptualization, Writing – review &editing.

**Data Availability**

All GWAS summary statistics analyzed in this study are publicly available for download by qualified researchers. The GWASs for LS-BMD, FA-BMD, TB-BMD and FN-BMD can be obtained through the IEU data portal (https://gwas.mrcieu.ac.uk/). The GWASs for constipation were provided by the FINNGEN (https://www.finngen.fi/en).

**Conflict of interest**

The authors declare no competing interests.

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