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ORIGINAL RESEARCH

# Effectiveness of Spironolactone in Reducing Osteoporosis and Future Fracture Risk in Middle-Aged and Elderly Hypertensive Patients

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**Objective:** While the role of aldosterone in bone metabolism is well established, the specific effects of the widely used aldosterone antagonist, spironolactone, on bone health are not fully understood. This study aimed to investigate the effects of spironolactone on osteoporosis and future fracture risk in middle-aged and elderly hypertensive patients, revealing its potential benefits for bone health.

**Methods:** Propensity score matching was employed in this study to create matched groups of spironolactone users and non-users at a 1:4 ratio. We investigated the association between spironolactone use and the risk of osteoporosis using multivariate logistic regression analysis. Furthermore, we conducted multivariate linear regression analysis to explore the relationship between cumulative dosage and the FRAX score. Subgroup analysis was also performed to assess the effects under different stratification conditions.

**Results:** In both pre-match and post-match analyses, multivariable logistic regression revealed a significant reduction in the risk of osteoporosis in the spironolactone usage group (pre-match: odds ratios [OR] 0.406, 95% confidence interval [CI], 0.280–0.588; post-match: OR 0.385, 95% CI, 0.259–0.571). Furthermore, post-match multivariable linear regression demonstrated a clear negative correlation between cumulative spironolactone dosage and the FRAX score. Subgroup analyses consistently supported these findings.

**Conclusion:** This study offers evidence supporting the significant positive impact of the antihypertensive drug spironolactone on bone health, resulting in a substantial reduction in the risk of osteoporosis and future fractures in hypertensive patients. Future research should consider conducting large-scale, multicenter, randomized controlled trials to further investigate the long-term effects of spironolactone on bone health in hypertensive patients.

**Keywords:** hypertensive, spironolactone, aldosterone, osteoporosis, FRAX score

## Introduction

Osteoporosis is a common systemic bone disease that results in weakened bones and an increased risk of fractures.[1] Hypertension and osteoporosis are two prevalent chronic diseases that often co-occur in middle-aged and older adults.[2] Globally, the reported incidence rate of hypertension is approximately 31%, while the incidence rate of osteoporosis can be as high as 21%.[3,4] As life expectancy increases, the incidence rates of both hypertension and osteoporosis are expected to rise, underscoring the growing healthcare challenge posed by these conditions in an aging global population.[5,6]

Hypertension is a risk factor for osteoporosis and osteoporotic fractures, significantly impacting morbidity and mortality in both men and women.[7,8] While lifestyle interventions are crucial for managing blood pressure (BP), pharmacological treatments play a more prominent role in reducing BP and the risk of atherosclerotic cardiovascular disease. Various types



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of antihypertensive medications are available, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and spironolactone, all of which are well-known inhibitors of the renin-angiotensin-aldosterone system (RAAS) and have demonstrated effective blood pressure control. Interestingly, an increasing body of cellular and animal research evidence suggests that localized activation of RAAS in bone tissue may contribute to osteoporosis.[9–11]

Effective prevention and treatment of osteoporosis have traditionally relied on increased vitamin D and calcium intake, bisphosphonates, and nasal spray calcitonin, with limited mention of spironolactone.[12–14] In recent years, a growing body of research has provided additional evidence supporting the notion that excessive aldosterone secretion within the RAAS system results in increased urinary calcium excretion. This disruption in calcium-phosphate metabolism ultimately elevates the risk of bone mineral loss.[15–18] Spironolactone, a crucial aldosterone receptor antagonist, effectively suppresses aldosterone secretion.[19] Animal experiments have shown that spironolactone can protect the skeletal health of rats with excessive aldosterone secretion.[20] Moreover, a study involving male congestive heart failure (CHF) patients suggested that spironolactone might have the potential to reduce the risk of fractures in this population.[21] However, despite being a vital antihypertensive medication, there has been no investigation to date into its long-term use in hypertensive patients or its potential impact on bone mineral density (BMD). Additionally, it remains unclear whether spironolactone can reduce the risk of osteoporosis and future fractures, leaving specific outcomes in this regard uncertain.

Therefore, the main aim of this study was to examine the potential impact of extended spironolactone use on the risk of osteoporosis and future fractures in middle-aged and elderly hypertensive patients. To confirm this finding, we will use propensity score matching to rigorously match spironolactone users and non-users in this study.

# Materials and Methods

## Study Population

### Inclusion Criteria

This study selected its participants from a pool of hypertensive patients who underwent BMD screening during hospitalization between January 2021 and December 2023. Initially, 2947 patients met the eligibility criteria.

### Exclusion Criteria

The selection process involved several exclusion criteria. Firstly, individuals younger than 40 years old were excluded. Subsequently, patients with a history of previous fractures were also excluded. Additionally, individuals diagnosed with various bone metabolism-related disorders, including hypogonadism, Cushing's syndrome, hyperthyroidism, hyperparathyroidism, as well as those with severe hepatic and renal disorders, were not considered for the study. Finally, individuals who had previously taken medications known to affect BMD were also excluded. After applying these criteria, a total of 2344 participants remained and were enrolled in the final study.

This study was approved by the Research Ethics Committee of the Xinjiang Uygur Autonomous Region People's Hospital (KY2022080905). All the procedures complied with the requirements of the Declaration of Helsinki. All participants provided informed written consent.

## Data Collection and Definitions

We collected demographic characteristics, clinical history, lifestyle details, physical examination findings, medication history, and laboratory data of the participants through electronic medical records. Detailed measurements, such as height, weight, body mass index (BMI), smoking status, and blood pressure, can be found in the Supplementary Materials. Table S1 shows the names of the various drugs. Laboratory parameters included measurements of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatinine (Cr), Alkaline Phosphatase (ALP), Thyroid Stimulating Hormone (TSH), as well as serum levels of potassium, calcium, phosphorus, Parathyroid Hormone (PTH), and 25-Hydroxyvitamin D. These measurements were conducted using a fully automated biochemical analyzer, and all hormone assessments followed current guidelines and were based on previous research conducted at our center.[22–24] Definitions for various diseases can be found in the Supplementary Materials.

## Medication Use and Cumulative Drug Dose

Following previous related studies, we categorized individuals as spironolactone users if they had taken spironolactone continuously for a minimum of 6 months in the past.[21,25] Information regarding participants' medication usage and duration was primarily extracted from their hospital records' medication history. The cumulative drug dose (in mg. months) was calculated as the daily dose (in mg) multiplied by the number of months.

## Outcomes

Based on dual-energy X-ray absorptiometry (DXA) scanning, BMD measurements were obtained. Detailed explanations about these measurements are provided in the Supplementary Materials. The unique Chinese FRAX assessment tool algorithm is used to determine the probability of experiencing a major osteoporotic fracture (MOF) or hip fracture (HF) within a 10-year period (www.shef.ac.uk./FRAX).[26,27] According to the latest guidelines, a BMD T-score of less than −1.0 at any site is considered as decreased bone mass, and a T-score of −2.5 or lower at any site indicates osteoporosis.[28–30]

## Propensity Score Matching

This study aimed to investigate the relationship between spironolactone use and osteoporosis. We employed propensity score matching, following the approach recommended by Lonjon et al.[31] The propensity score, representing the likelihood of each patient using spironolactone, was generated using a logistic regression model. Our matching variables in the propensity score model included sex, age, BMI, menopausal status, and all antihypertensive and antidiabetic medications. Spironolactone users and non-users were matched using the nearest neighbor method at a 1:4 ratio based on the logit scale. The caliper width was limited to within 0.2 standard deviations, and the matching process was conducted without replacement. To assess the balance between variables in each group before and after matching, we utilized the Standardized Mean Difference (SMD), with an SMD value below 0.10 indicating a balanced distribution.[32,33]

## Statistical Analysis

We categorized study participants into two groups: the spironolactone users group and the non-users group, based on their spironolactone usage. We checked for multicollinearity using variance inflation factors (VIFs), and a VIF value of less than 10 for each variable indicated the absence of multicollinearity (Table S2 and Figure S1). To analyze the relationship between cumulative spironolactone dose and BMD and FRAX scores, we conducted multiple linear regression. Furthermore, we performed multiple logistic regression analyses to compare the risk of decreased bone mass and osteoporosis between the two groups. To assess dose-response relationships, we utilized restricted cubic spline (RCS) analysis, with additional two-stage comparisons based on the turning points of the RCS curves. Finally, to demonstrate the robustness of our results, we conducted both subgroup analysis and sensitivity analysis. For detailed statistical analyses, please refer to the Supplementary Materials.

All data were analyzed using R 4.2.2. Statistical significance was accepted for two-sided $P < 0.05$.

# Results

## Patient Selection

Figure 1 illustrates the participant selection process, with a total of 1300 participants being finalized for inclusion in our analysis after 1:4 matching (260 participants in the use group and 1040 participants in the non-use group).

## Baseline Characteristics Before and After Propensity Score Matching

Table 1 displays the baseline characteristics before and after matching. Among all participants, individuals using spironolactone exhibited relatively higher levels of BMI, serum calcium, and TSH compared to non-users. Conversely, they had lower levels of serum potassium and ALP. In this group, rates of menopause and diabetes mellitus (DM) were comparatively lower, but there was a significantly higher prevalence of primary aldosteronism (PA). Additionally, these individuals were more likely to be taking various medications, including antihypertensives, lipid-lowering drugs, and

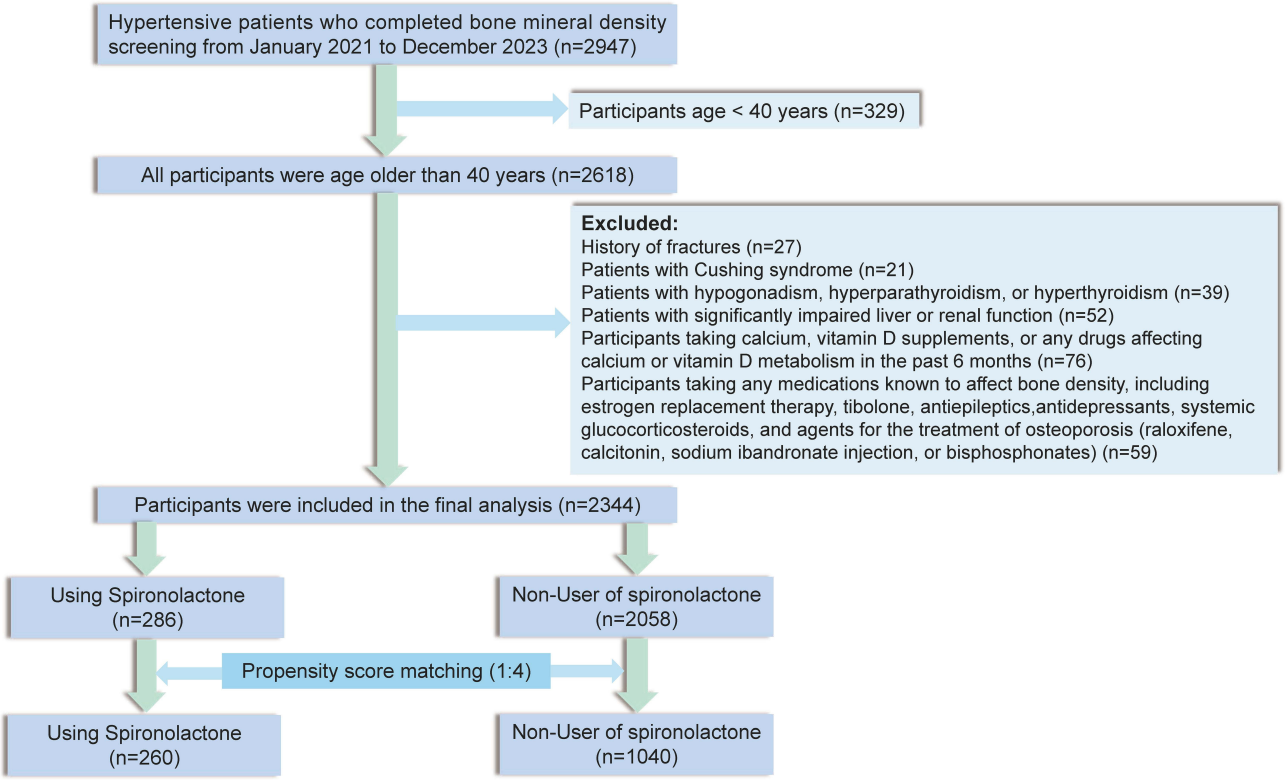


**Figure 1** Flow chart of patient selection.

antiplatelet agents. The matching improved variable balance, with an absolute SMD < 0.10. The balance before and after propensity score matching is shown in Figure S2.

## Relationship Between the Use of Spironolactone and Reduced Bone Mass and Osteoporosis (User Vs Non-User)

Before matching, participants using spironolactone demonstrated a significantly lower risk of reduced bone mass compared to non-users, as evidenced in both Model 1 and the fully adjusted Model 4 (Table S3). This protective effect of spironolactone also extended to osteoporosis, where users exhibited a 60% lower risk of developing the condition compared to non-users (odds ratio [OR], 0.406; 95% confidence interval [CI], 0.280–0.588) (Table 2). After the matching process, the analysis consistently indicated a reduced risk of reduced bone mass among spironolactone users (OR, 0.371; 95% CI, 0.273–0.503) (Table S4). Furthermore, the negative correlation with osteoporosis was further supported by the results from Model 1 and the fully adjusted Model 4, which yielded ORs of 0.434 (95% CI, 0.294–0.624) and 0.385 (95% CI, 0.259–0.571), respectively (Table 3).

## Relationship Between Cumulative Drug Doses and BMD and FRAX Scores

Multivariate linear regression analysis revealed a significant positive correlation between the cumulative dose of spironolactone and BMD at various sites, a correlation that remained significant even after adjustments in multivariable Model 4 (Table S5). Furthermore, concerning the risk of future fractures, we observed a consistent trend where an increase in the cumulative dose of spironolactone was associated with a reduced risk of future fractures (MOF and HF) across all models (Table 4). This consistent pattern observed in different analyses suggests that higher doses of spironolactone may have a protective effect on bone health.

**Table 1** Baseline Characteristics Before and After Propensity Score Matching

| Characteristic | Before Propensity Score Matching | | | After Propensity Score Matching | | |
|---|---|---|---|---|---|---|
| | Non-user (N=2058) | User (N=286) | SMD | Non-user (N=1040) | User (N=260) | SMD |
| Age | 56.43±10.87 | 56.99±10.87 | 0.051 | 57.42±11.17 | 56.72±10.68 | 0.064 |
| Female (%) | 1044 (50.73%) | 158 (55.24%) | 0.091 | 560 (53.85%) | 141 (54.23%) | 0.018 |
| BMI (kg/m$^2$) | 27.05±3.74 | 27.42±3.36 | 0.104 | 27.18±3.79 | 27.30±3.26 | 0.036 |
| SBP (mmHg) | 145.15±17.45 | 143.50±18.27 | 0.092 | 145.37±18.43 | 143.72±17.98 | 0.091 |
| DBP (mmHg) | 86.76±12.57 | 85.52±13.62 | 0.095 | 86.33±13.07 | 86.06±13.74 | 0.020 |
| Current smoking (%) | 524 (25.46%) | 60 (20.98%) | 0.106 | 241 (23.17%) | 55 (21.15%) | 0.024 |
| Menopausal (%) | 812 (39.46%) | 98 (34.27%) | 0.267 | 360 (34.62%) | 92 (35.38%) | 0.070 |
| **Laboratory tests** | | | | | | |
| Serum potassium (mmol/L) | 3.90±0.34 | 3.81±0.36 | 0.248 | 3.89±0.33 | 3.81±0.36 | 0.215 |
| PTH (pg/mL) | 49.90 (35.80–68.68) | 51.90 (40.45–66.20) | 0.085 | 52.33 (38.20–70.28) | 50.90 (39.60–65.90) | 0.071 |
| Serum calcium (mmol/L) | 2.28±0.30 | 2.32±0.37 | 0.119 | 2.29±0.30 | 2.33±0.38 | 0.111 |
| 25-hydroxyvitamin D (nmol/L) | 19.61 (12.39–29.50) | 17.60 (11.35–27.45) | 0.075 | 18.91 (12.01–28.58) | 17.75 (11.30–27.80) | 0.012 |
| Serum phosphorus (mmol/L) | 1.16±0.17 | 1.15±0.16 | 0.067 | 1.16±0.17 | 1.15±0.16 | 0.033 |
| ALT (U/L) | 23.43 (16.20–36.00) | 22.00 (16.00–36.30) | 0.019 | 23.00 (16.00–33.00) | 22.05 (16.60–37.00) | 0.092 |
| AST (U/L) | 20.30 (16.71–26.00) | 20.00 (16.45–25.00) | 0.043 | 20.20 (16.90–25.56) | 20.00 (16.64–25.28) | 0.005 |
| Cr (umol/L) | 64.65±15.98 | 66.03±15.45 | 0.088 | 65.70±16.60 | 65.46±15.31 | 0.015 |
| ALP (U/L) | 83.49±28.28 | 78.88±30.15 | 0.158 | 77.99 (61.70–97.00) | 79.12 (57.00–103.00) | 0.008 |
| TSH (uIU/mL) | 2.15 (1.42–3.34) | 2.44 (1.74–3.33) | 0.106 | 2.23 (1.45–3.33) | 2.38 (1.71–3.33) | 0.060 |
| Urea (umol/L) | 330.93±94.60 | 331.43±94.62 | 0.005 | 331.02±96.28 | 328.88±92.98 | 0.023 |
| **Medical history** | | | | | | |
| PA (%) | 171 (8.31%) | 138 (48.25%) | 1.112 | 102 (9.81%) | 130 (50.00%) | 1.097 |
| DM (%) | 669 (32.51%) | 54 (18.88%) | 0.316 | 218 (20.96%) | 54 (20.77%) | 0.005 |
| CHD (%) | 153 (7.43%) | 22 (7.69%) | 0.010 | 83 (7.98%) | 19 (7.31%) | 0.019 |
| **Medications** | | | | | | |
| Statins (%) | 381 (18.51%) | 104 (36.36%) | 0.408 | 323 (31.06%) | 75 (28.85%) | 0.049 |
| Diuretics (%) | 200 (9.72%) | 62 (21.68%) | 0.333 | 178 (17.12%) | 51 (19.62%) | 0.063 |
| Beta-blockers (%) | 345 (16.76%) | 80 (27.97%) | 0.271 | 255 (24.52%) | 58 (22.31%) | 0.063 |
| Calcium channel blockers (%) | 1069 (51.94%) | 198 (69.23%) | 0.359 | 700 (67.31%) | 172 (66.15%) | 0.013 |
| ACEIs/ARBs (%) | 824 (40.04%) | 168 (58.74%) | 0.381 | 586 (56.35%) | 140 (53.85%) | 0.053 |
| Antihyperglycemic drug (%) | 566 (27.50%) | 48 (16.78%) | 0.260 | 194 (18.65%) | 47 (18.08%) | 0.003 |
| **DXA BMD T-scores** | | | | | | |
| Lumbar 1 | −0.93±1.56 | −0.08±1.77 | 0.507 | −0.90±1.57 | −0.05±1.77 | 0.505 |
| Lumbar 2 | −0.87±1.58 | −0.02±1.66 | 0.527 | −0.85±1.61 | 0.01±1.65 | 0.531 |
| Lumbar 3 | −0.84±1.64 | 0.06±1.69 | 0.541 | −0.79±1.65 | 0.09±1.68 | 0.534 |
| Lumbar 4 | −0.73±1.66 | 0.11±1.78 | 0.487 | −0.68±1.67 | 0.12±1.76 | 0.467 |
| Neck | −0.86±1.07 | −0.58±0.92 | 0.280 | −0.87±1.07 | −0.57±0.92 | 0.301 |
| Wards | −1.12±1.20 | −0.95±1.06 | 0.148 | −1.13±1.18 | −0.94±1.06 | 0.171 |
| Total | −0.20±1.08 | 0.04±0.95 | 0.235 | −0.19±1.10 | 0.05±0.95 | 0.234 |
| **FRAX scores (%)** | | | | | | |
| MOF | 3.69±2.83 | 3.08±1.80 | 0.257 | 3.66±2.80 | 3.03±1.78 | 0.267 |
| HF | 1.47±2.24 | 0.99±1.37 | 0.256 | 1.46±2.24 | 0.97±1.37 | 0.264 |
| **Outcomes** | | | | | | |
| Decreased bone mass | 1517 (73.75%) | 162 (56.64%) | 0.350 | 765 (73.56%) | 144 (55.38%) | 0.380 |
| Osteoporosis (%) | 531 (25.81%) | 38 (13.29%) | 0.320 | 264 (25.38%) | 33 (12.69%) | 0.322 |

**Notes**: Data are presented as mean ± standard deviation, median (interquartile range), or as numbers, and percentages.

**Abbreviations**: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; ALT, alanine transaminase; AST, aspartate transaminase; Cr, creatinine; ALP, alkaline phosphatase; TSH, thyroid stimulating hormone; PA, primary aldosteronism; DM, diabetes mellitus; CHD, coronary heart disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; Neck, neck of the femur; Wards, Ward's triangle; Total, total femur; MOF, major osteoporotic fracture; HF, hip fracture, SMD Standardized Mean Difference.

**Table 2** Effect of User versus Non-User on Osteoporosis Before Matching

| Exposure | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) | Model 4 OR (95% CI) |
|---|---|---|---|---|
| Non-user | Reference | Reference | Reference | Reference |
| User | 0.440 (0.261, 0.703) | 0.424 (0.249, 0.683) | 0.395 (0.231, 0.642) | 0.406 (0.280, 0.588) |

**Notes**: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, and smoking status were adjusted. Model 3: Model 2 plus adjustment for serum potassium, PTH, serum calcium, serum phosphorus, and ALP. Model 4: Model 3 plus adjustment for the the use probability of spironolactone.
**Abbreviations**: OR, odds ratio; CI, confidence interval; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

**Table 3** Effect of User versus Non-User on Osteoporosis After Matching

| Exposure | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) | Model 4 OR (95% CI) |
|---|---|---|---|---|
| Non-user | Reference | Reference | Reference | Reference |
| User | 0.434 (0.294, 0.624) | 0.430 (0.290, 0.622) | 0.386 (0.257, 0.566) | 0.385 (0.259, 0.571) |

**Notes**: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, and smoking status were adjusted. Model 3: Model 2 plus adjustment for serum potassium, PTH, serum calcium, serum phosphorus, and ALP. Model 4: Model 3 plus adjustment for the the use probability of spironolactone.
**Abbreviations**: OR, odds ratio; CI, confidence interval; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

**Table 4** The Relationship Between Cumulative Drug Dose and FRAX Score

| Exposure | Model 1 β (95% CI) | Model 2 β (95% CI) | Model 3 β (95% CI) | Model 4 β (95% CI) |
|---|---|---|---|---|
| **MOF** | | | | |
| Cumulative dose (per 100 mg.months increase) | −0.076 (−0.099, −0.052) | −0.068 (−0.090, −0.046) | −0.037 (−0.054, -0.012) | −0.035 (−0.056, −0.014) |
| **HF** | | | | |
| Cumulative dose (per 100 mg.months increase) | −0.041 (−0.059, −0.022) | −0.034 (−0.052, −0.016) | −0.010 (−0.024, −0.010) | −0.007 (−0.027, −0.007) |

**Notes**: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, and smoking status were adjusted. Model 3: Model 2 plus adjustment for serum potassium, PTH, serum calcium, serum phosphorus, and ALP. Model 4: Model 3 plus adjustment for the the use probability of spironolactone.
**Abbreviations**: MOF, major osteoporotic fracture; HF, hip fracture; β, regression coefficient; CI, confidence interval; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

## Relationship Between Cumulative Drug Dose, Reduced Bone Mass, and Osteoporosis

We investigated the dose-response relationship between cumulative drug dose and the risks of decreased bone mass and osteoporosis using RCS. Figure S3 illustrates that when cumulative dosages exceed 370 mg.months, participants experience increased BMD and a reduced risk of decreased bone mass (Tables S6 and S7). A similar pattern was observed with osteoporosis; as illustrated in Figure 2, osteoporosis risk diminishes when the cumulative drug dose surpasses 400 mg.months. The analysis of these turning points reveals that cumulative drug doses above 400 mg.months are associated with a significant increase in BMD and a lower risk of osteoporosis compared to lower dosages (Tables 5 and S8). These results further highlight the beneficial effects of spironolactone on bone health and may reduce the incidence of osteoporosis.

## Subgroup Analysis and Sensitivity Analysis

In our subgroup analyses, we stratified participants based on factors including sex, age, BMI, smoking status, DM, and menopausal status. Across these subgroups, we observed consistent outcomes with respect to both reduced bone mass and osteoporosis (Figures 3 and S4). Furthermore, when we conducted additional stratification by the type of medication used,

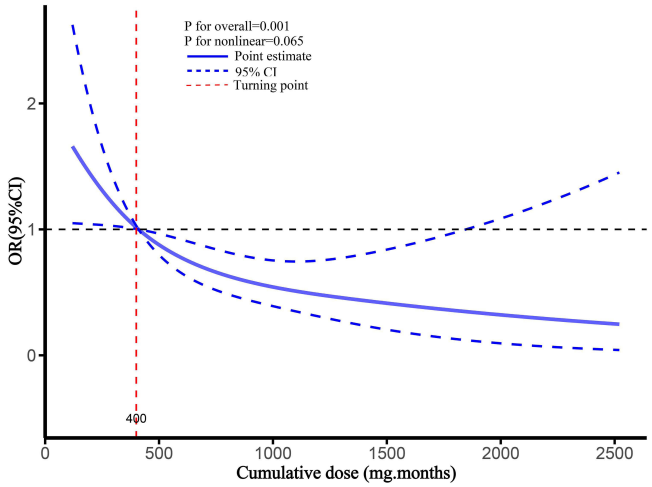


**Figure 2** Dose-response relationship between cumulative drug dose and osteoporosis.

this consistency remained (Figures 4 and S5). Finally, in the sensitivity analysis, participants with PA were excluded, and the results remained essentially unchanged, whether conducted before or after matching (Tables S9–S12). These findings collectively suggest that spironolactone has a positive impact on bone mass across various circumstances.

## Discussion

The results of the present study reveal a significant association between spironolactone use and both reduced bone mass and a lower risk of osteoporosis in middle-aged and elderly hypertensive patients. This association remained consistent across various subgroup analyses, underscoring the robustness of our findings. Furthermore, we observed a significant and positive correlation between the cumulative dose of spironolactone and BMD at all assessed sites, coupled with a reduced risk of future fractures. These combined findings emphasize that spironolactone, as an antihypertensive medication, offers substantial benefits to skeletal health and effectively mitigates the risk of osteoporosis.

Numerous previous studies have highlighted aldosterone's crucial role in regulating calcium and phosphorus metabolism.[34–36] These studies reveal a bidirectional interaction between aldosterone and PTH, where aldosterone significantly increases urinary calcium excretion, subsequently stimulating PTH secretion. Furthermore, PTH enhances aldosterone secretion both by elevating calcium concentrations in adrenal glomerular zone cells and through angiotensin II induction. This interaction leads to continuous calcium loss from the body, ultimately resulting in persistent bone mass reduction.[37] In an experimental animal study on primary aldosteronism, researchers not only observed mineral loss but also noted a progressive decrease in cortical bone strength.[11] These adverse effects, however, were effectively mitigated by spironolactone treatment.[38,39] A similar US study involving male patients with CHF indicated that spironolactone administration was negatively associated with fracture occurrence, suggesting its potential in reducing fracture risk.[21]

**Table 5** The Impact of Cumulative Dose Before and After the RCS Turning Point on Osteoporosis

| Osteoporosis | OR (95% CI) | P value |
|---|---|---|
| Turning point (mg.months) | 400 | |
| Cumulative dose < 400 mg.months | Reference | |
| Cumulative dose > = 400 mg.months | 0.337 (0.204, 0.543) | <0.001 |

**Notes**: Age, sex, BMI, smoking status, serum potassium, PTH, serum calcium, serum phosphorus, ALP, and the use probability of spironolactone were adjusted.
**Abbreviations**: RCS, restricted cubic splines; OR, odds ratio; CI, confidence interval; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

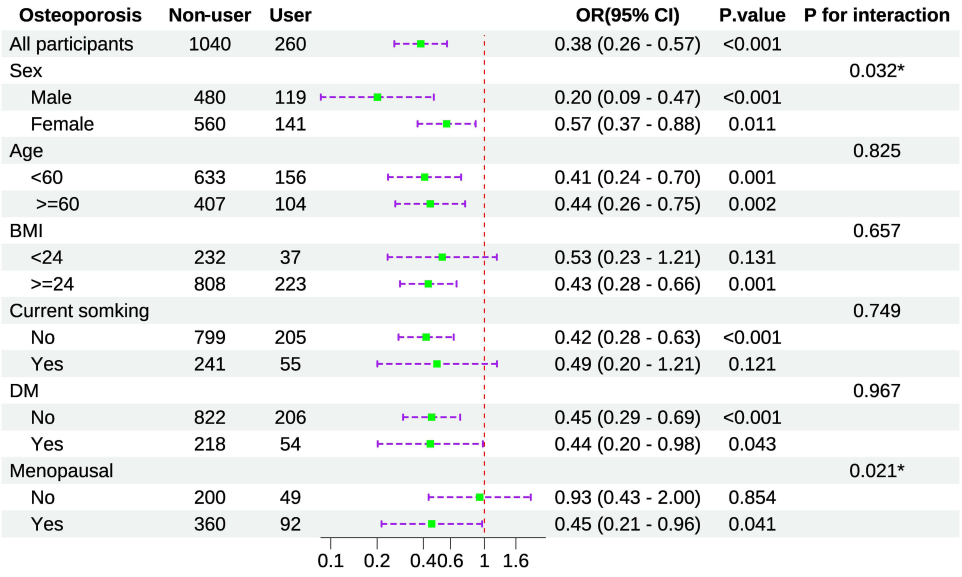


**Figure 3** Association between cumulative drug dose and osteoporosis in various subgroups.

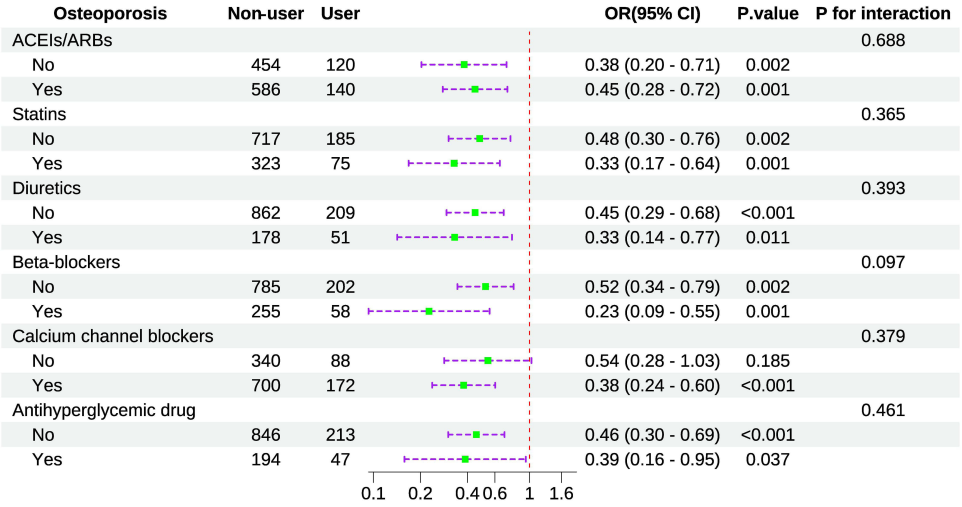


**Figure 4** Association between cumulative drug dose and osteoporosis in medication subgroups.

Spironolactone has historically been regarded as an essential antihypertensive drug that plays a crucial role in managing blood pressure and treating HF.[19,40,41] It is also linked to potential therapeutic benefits in stroke and cardiovascular disease, with a cohort study demonstrating that its administration and cumulative doses significantly lower stroke risks in hypertensive patients.[42] Recent studies have suggested that spironolactone might positively affect bone health, although these investigations have largely been confined to animal models.[38,39,43] This leaves the drug's effects on bone health in humans, particularly its long-term impact on osteoporosis and fracture prevention in hypertensive patients, largely unexplored. Our study fills this gap by confirming spironolactone's protective effect on BMD, highlighting its significant role in mitigating the risk of osteoporosis and future fractures in middle-aged and elderly hypertensive patients.

In our stratified analyses, we uncovered a notable finding: spironolactone's effectiveness was significantly higher in menopausal women than in non-menopausal women. This difference in response may stem from the reduced levels of estrogen post-menopause, which tends to obscure spironolactone's effects in non-menopausal women.[44] It's essential to

recognize the pivotal role of estrogen in managing calcium and phosphorus metabolism.[45–47] A decline in estrogen levels after menopause can cause an increase in bone resorption alongside a decrease in bone formation.[47,48] This reduction in estrogen consequently leads to a lower bone mineral density, potentially progressing to osteoporosis. Nevertheless, further basic research is required to solidify our understanding of the precise causes and mechanisms behind these observations.

Our findings suggest that spironolactone's beneficial effects on bone health can be attributed to multiple mechanisms. Initially, spironolactone modulates aldosterone action, a hormone crucial for calcium and phosphorus metabolism, thereby potentially improving bone health.[15,16,19] Additionally, it diminishes urinary calcium loss, aiding in the preservation of calcium balance within the body, a fundamental aspect of maintaining bone strength.[49,50] Furthermore, the antiandrogenic properties of spironolactone may indirectly enhance estrogen metabolism, thereby elevating estrogen levels and mitigating bone loss in postmenopausal women.[44,51,52] Moreover, spironolactone contributes to an increase in blood potassium levels. Research indicates that adequate potassium intake can prevent fractures, thus offering protective benefits for bones.[53–55]

This study is the first to explore the link between spironolactone use and the risk of osteoporosis and future fractures in middle-aged and elderly hypertensive patients, marking a significant transition from laboratory research to clinical application. Its strengths lie in the comprehensive clinical data utilized, ensuring the reliability of results through propensity score matching to minimize group discrepancies, and the employment of two-stage comparisons and subgroup analyses for in-depth evaluation. In interpreting the results of this study, it is important to acknowledge its limitations. The cross-sectional research design precludes establishing causality. Although propensity score matching and multivariate analyses were used, there remains the possibility of residual bias and unmeasured confounding factors. Additionally, the reliance on medical record systems for medication information may introduce information bias. Crucially, the study did not include data on sex hormone levels, which are influential in bone metabolism. Lastly, the study's findings, based solely on Chinese hypertensive patients, may not be generalizable to other populations without careful consideration.

## Conclusion

In conclusion, this study demonstrates that the antihypertensive drug spironolactone has a significant impact on the bone health of middle-aged and elderly hypertensive patients. It notably reduces the risk of osteoporosis and future fractures. This finding has substantial implications for clinical practice, suggesting that spironolactone could be a valuable therapeutic option not only for managing hypertension but also for mitigating the associated risks of bone health deterioration. Given the limitations of cross-sectional studies and the specific study population, larger prospective randomized controlled trials are warranted to further confirm these observations.

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## Disclosure

The authors report no conflicts of interest in this work.

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