Gender-Difference Association Between Blood Pressure And Osteoporosis: Results From Henan Rural Cohort Study

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Research Article

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Abstract

Purpose: Accumulating researches have observed the potential association between osteoporosis and hypertension, however, the evidence regarding gender-difference association between divergent proxies of blood pressure and osteoporosis was limited in rural areas.

Methods: A total of 7689 participants enrolled from Henan Rural Cohort study were included in this research. Four proxies (systolic blood pressure (SBP); diastolic blood pressure (DBP); mean arterial pressure (MAP); pulse pressure (PP)) of blood pressure were measured. The association between blood pressure and osteoporosis was assessed by binary logistic regression with adjustment of potential influencing factors. All analyses were stratified by gender. To test the robust of results, similar analyses were also conducted in non-hypertension participants and postmenopausal women.

Results: The significantly positive association between hypertension and osteoporosis was observed among women but not in men. Increasing blood pressure corresponded with prevalent osteoporosis among women, in which each 10 mmHg increase in SBP, MAP, and PP corresponded with 1.07-fold (1.03, 1.12), 1.14-fold (1.07, 1.21), and 1.08-fold (1.02, 1.15) prevalence of osteoporosis, respectively. This positive association was still significant among non-hypertension women and postmenopausal women, but not in pre-menopausal women.

Conclusion: In rural areas, there was a positive association between blood pressure and prevalent osteoporosis in women, but not in men. Menopausal status may be responsible for this gender-difference.

Introduction

As a disruptive condition characterized by bone mass reduction and bone architectural deterioration, osteoporosis often results in bone fragility and high fracture risk [1–2]. In China, the recently reported prevalence of osteoporosis was 13.5% in men and 29.0% in women [3], which was fueled markedly increased by drastic aging population [4]. By 2050, an estimated 60 to 120 million people would suffer from osteoporosis [5], which results in 5.99 million osteoporosis fractures costing 25.43 billion dollars [6]. Unexpected cost imposes an enormous economic burden on society and family, especially in rural areas due to the limited medical resources [4].

Raised blood pressure, a leading risk factor for global death and disability [7], accounts for 10.4 million deaths worldwide [8]. Over the past few years, attention has been paid to the association between osteoporosis and blood pressure owing to their common regulating mechanisms [9]. Previous epidemiological studies have reported that high blood pressure was associated with increased bone loss and decreased bone turnover [10–11]. Conducted in 270 postmenopausal Turkish women, a cross-sectional study indicated that hypertension was related with low bone mineral density (BMD). A meta-analysis including 1430431 participants and 148048 osteoporotic fracture cases also found the risk of osteoporosis fractures was higher among people with hypertension than those without [12]. However, this

plausible association may be dissimilar by gender. A longitudinal study reported that hypertension corresponded with high femoral neck BMD in men but with low in women, and the significant association between hypertension and osteoporosis fractures was only observed in women [13]. In additionally, previous meta-analysis also observed the similar result, which the association between hypertension and osteoporosis was stronger in women than in men [12].

Despite these accumulating studies provide comprehensive results regarding association between hypertension and osteoporosis, the evidence among rural population was scare. In addition, the association between specific proxy of blood pressure (systolic blood pressure (SBP); diastolic blood pressure (DBP); mean arterial pressure (MAP); pulse pressure (PP)) and osteoporosis was also limited provided. Thus, this research hypothesized that the association between blood pressure and osteoporosis differed across gender, and aimed to assess these associations among rural population.

Methods

Study participants

Participants in this research were selected from Henan Rural Cohort study (Register number: ChiCTR-OOC-15006699). More details were published previously [14]. Briefly, the Henan Rural Cohort study recruited 39259 subjects aged 18–79 years at baseline from five Henan rural countries (Suiping, Yuzhou, Xinxiang, Tongxu, and Yima). It was designed to investigate the prevalence of non-communicated diseases (e.g., hypertension, stroke, or osteoporosis) in Chinese rural population, and to access the association of environmental exposures and genetics with non-communicated diseases. Eligibility criterion included the subjects were permanent residents, were healthier as to answer our questionnaire, and did not move out in the following-up.

Among 39259 subjects in the baseline, only 8475 subjects were carried out bone mineral density (BMD) detection [15]. Considering the disturbed effect of homeostasis imbalance on bone metabolism, we excluded the patients who had stroke, cancers, and kidney failure. We also excluded participants with missing blood pressure measurements. Finally, 7689 subjects were included in the final analyses. The study protocol was approved by the Zhengzhou University Life Science Ethics Committee (Code: [2015] MEC (S128)), and all the participants provided informed consent.

Covariate measurement

Baseline information of participants including sociodemographic characteristics (age and gender), socioeconomic status (educational level, marital status, average monthly income), and lifestyles (smoking and drinking status, physical activity, diets) were collected via a structured questionnaire by trained investigator [16]. Specifically, age was divided into 18-, 45-, and 65- years; educational level were divided into elementary school or below, junior school, and high school or above; marital status was divided into married/cohabitation and unmarried/divorced/widowed; average monthly income was divided into <¥500, ¥500-, and ¥1000-; both smoking- and drinking status were divided into never, former,

and current; physical activity measured by metabolic equivalent (MET) hours per week was classified into low, moderate, and high [17]; more vegetables and fruits intake was defined as one person who ate vegetables and fruits over 500 g/day averagely and high fat diet was defined as one person who ate fat over 75 g/day averagely; body mass index (BMI) was calculated by height and weight, which were measured to the nearest 0.1cm and 0.1kg through standard measuring equipment, respectively.

Measurement of blood pressure and definition of hypertension

SBP and DBP were measured by using electronic sphygmomanometers (Omron HEM-7071A, Japan). Participants were asked to rest for at least 5 minutes before measurement, and then test three times on the right arm at heart-level sitting position in measuring. MAP was calculated as 2/3 DBP plus 1/3 SBP. PP was calculated as SBP minus DBP. Hypertension was defined as mean SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, or a self-reported history of hypertension, or had taken antihypertensive drugs in the last two weeks [18].

Definition of osteoporosis

The calcaneus BMD of participants was measured by the trained staff who was blind to the study, with a Sahara clinical bone densitometer (Hologic, USA). Participants were asked to sit down with their hip bent about 90 degrees, knees about 40 degrees, and ankles about 10 degrees, and the left heel was measured three times. If the subject had previously fractured the measured heel, the otherwise heel would be measured. T-score was calculated as the difference of the subject BMD and the mean BMD of healthy adults divided by the young adult standard deviation (SD). The BMD of healthy adult and SD of young adult were derived from a reference database provided by the manufacturer. According to the World Health Organization (WHO) classification criteria, individual was defined as osteoporosis if T-score ≤-2.5 [19].

Statistical analysis

Considering that a potential gender-difference association between osteoporosis and blood pressure may exist, all analyses in this research were presented by gender. Continuous variables were expressed as mean ± SD and categorical variables were expressed as counts with percentages. Gender-difference characteristics were detected by using one-way ANOVA or Pearson's chi-square test. Blood pressure indicators were divided into five groups by each 10-mmHg increase, and the lowest group was set as the reference group. The prevalence of osteoporosis was presented by gender and blood pressure group and unadjusted binary logistic regression were employed to detect the trend. With adjustment of age, gender, educational level, marital status, average monthly income, smoking, drinking status activity, high-fat diet, fruits and vegetables intake, and BMI, binary logistic regression model was utilized to explore the associations between osteoporosis and blood pressure. To test the robustness of our findings, a sensitivity analysis excluding participants with hypertension was completed. Considering menopause status usually related with osteoporosis [20], a stratified analysis among women by menopause status

were also conducted. It should be noted that 2687 participants were postmenopausal women and 1467 were premenopausal women, because the missing menopause status.

All analyses were conducted via R software version 4.0.3. All tests were two-tailed and $P < 0.05$ was regarded as statistically significant.

Results

Baseline characteristics of participants

A total of 2879 (37.44%) men and 4810 (37.44%) women were included in this research. There were 405 (14.07%) participants in men and 1089 (62.56%) participants in women were identified with osteoporosis. Compared with men, women were more likely to be older, lower educational, higher average monthly income, never smoking or drinking, lower physical activity, lower high fat diet, more vegetables and fruits intake, and higher BMI (all $P < 0.05$). Additionally, women had lower SBP (121.72 ± 18.94 *vs.* 122.64 ± 17.58 mmHg), DBP (74.97 ± 10.86 *vs.* 76.52 ± 11.32 mmHg), and MAP (90.56 ± 12.78 *vs.* 91.89 ± 12.73 mmHg) but higher PP (46.75 ± 12.53 *vs.* 46.12 ± 10.89 mmHg) than men (all $P < 0.05$). More details were presented in Table 1.

Table 1
Baseline characteristics of participants by gender.

Variables	Total	Men	Women	*P*
	N = 7689	N = 2879	N = 4810	
Agegrp, n (%)				< 0.001
18-	1137(14.79)	365 (12.68)	772(16.05)	
45-	4889(63.58)	1766(61.34)	3123(64.93)	
65-	1663(21.63)	748(25.98)	915(19.02)	
Educational level, n (%)				< 0.001
Elementary school or below	3377(43.92)	949(32.96)	2428(50.48)	
Junior high school	3181(41.37)	1348(46.82)	1833(38.11)	
High school or above	1131(14.71)	582(20.22)	549(11.41)	
Marital status, n (%)				0.138
Married/cohabitating	7011(91.18)	2643(91.80)	4368(90.81)	
Unmarried/divorced /widowed	678(8.82)	236(8.20)	442(9.19)	
Average monthly income, n (%)				
<500 RMB	2444(31.79)	985(34.21)	1459(30.33)	
500–1000 RMB	2323(30.21)	854(29.66)	1469(30.54)	
≥1000 RMB	2922(38.00)	1040(36.12)	1882(39.13)	
Smoking status, n (%)				< 0.001
Never	5689(74.90)	932(32.99)	4757(99.73)	
Former	364(4.79)	358(12.67)	6(0.13)	
Current	1542(20.30)	1535(54.34)	7(0.15)	
Drinking status, n (%)				< 0.001
Never	5918(77.90)	1303(46.12)	4615(96.71)	
Former	1077(14.18)	951(33.66)	126(2.64)	

Abbreviations: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure.

Variables	Total	Men	Women	*P*
	N = 7689	N = 2879	N = 4810	
Current	602(7.92)	571(20.21)	31(0.65)	
Physical activity, n (%)				< 0.001
Low	2151(27.98)	917(31.85)	1234(25.65)	
Moderate	2961(38.51)	819(28.45)	2142(44.53)	
High	2577(33.52)	1143(39.70)	1434(29.81)	
High fat diet, n (%)	1552(20.18)	783(27.20)	769(15.99)	< 0.001
More vegetables and fruits intake, n (%)	4060(52.80)	1571(54.57)	2489(51.75)	0.016
Hypertension, n (%)	1932(25.13)	694(24.11)	1238(25.74)	0.110
Osteoporosis, n (%)	1494(19.43)	405(14.07)	1089(22.64)	< 0.001
Postmenopausal women, n (%)	2687(34.95)	-	2687(55.86)	-
BMI (kg/m^2, mean ± SD)	24.65 ± 3.42	24.39 ± 3.37	24.80 ± 3.44	< 0.001
SBP (mmHg, mean ± SD)	122.07 ± 18.44	122.64 ± 17.58	121.72 ± 18.94	0.034
DBP (mmHg, mean ± SD)	75.55 ± 11.06	76.52 ± 11.32	74.97 ± 10.86	< 0.001
MAP (mmHg, mean ± SD)	91.06 ± 12.78	91.89 ± 12.73	90.56 ± 12.78	< 0.001
PP (mmHg, mean ± SD)	46.51 ± 11.95	46.12 ± 10.89	46.75 ± 12.53	0.027

Abbreviations: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure.

Prevalence of osteoporosis in different blood pressure groups

Figure 1 exhibits the changes in prevalence of osteoporosis in different blood pressure groups. In SBP subgroups, the prevalence of osteoporosis increased from 16.89% in ≤ 110 mmhg group to 30.30% in 140- mmHg among women (P_{treand} <0.001), while the same trend was not found in men (from 16.45–18.52%, P_{treand} =0.823). With increasing DBP, the prevalence of osteoporosis decreased from 18.13% in ≤ 60 mmHg group to 16.41% in 90- mmHg among men (P_{treand} <0.001), while the same trend was not

found in women (from 26.12–22.27%, P_{treand} =0.094). In MAP subgroups, the prevalence of osteoporosis increased from 19.17% in ≤ 80 mmhg group to 25.41% in 110- mmHg among women (P_{treand} <0.001), while the same trend was not found in men (from 18.53–18.75%, P_{treand} =0.182). With increasing PP, the sharply increased trend of prevalence was only observed in women (from 11.56% in ≤ 30 mmhg group to 34.95% in 60- mmHg, P_{treand} <0.001). As shown in **Supplementary table 1**, the crude prevalence of osteoporosis among hypertension (22.88% in total, 14.99% in men, 27.30% in women) was slightly higher than this among non-hypertension (18.27% in total, 13.78% in men, 21.02% in women).

Gender-difference association between blood pressure and osteoporosis

As shown in Fig. 2, with adjustment of age, gender, educational level, marital status, average monthly income, smoking, drinking status activity, high-fat diet, fruits and vegetables intake, and BMI, participants identified with hypertension was related to a 1.22-fold (1.06–1.40), 1.30-fold (0.99,1.69), and 1.19-fold (1.01–1.41) risk for prevalent osteoporosis among total population, men, and women, respectively, compared with non-hypertension participants. Among total population, each 10 mmHg increase in SBP, DBP, MAP, and PP corresponded with 7% (3%-10%), 6% (0–12%), 12% (6%-18%), and 8% (3%-13%) increased in prevalence of osteoporosis, respectively. However, these significantly positive associations between blood pressure and osteoporosis were not observed among men (All $P > 0.05$). Among women, the odds ratios (ORs) of each 10 mmHg increase in SBP, MAP, and PP for osteoporosis were 1.07 (1.03,1.12), 1.08 (1.02,1.15), and 1.14 (1.07,1.21), respectively. Compared individuals with lower blood pressure (with SBP ≤ 110 mmHg, DBP ≤ 60 mmHg, MAP ≤ 80 mmhg, PP ≤ 30 mmHg), men with higher DBP (90- mmHg) or MAP (110- mmHg) and women with higher SBP (140- mmHg) or PP (60- mmHg) had a higher risk for prevalent osteoporosis, the corresponding ORs were 1.76 (1.03,3.06), 1.61 (1.05,2.44), 1.45 (1.15,1.83), and 1.77 (1.17,2.75). More details were presented in **Supplementary table 2**.

Sensitivity analyses

Figure 3 exhibits the results of sensitivity analyses. Among non-hypertension participants, each 10 mmHg increase in SBP and PP correspond with 1.09-fold (1.01–1.18), 1.15-fold (1.03,1.27) risk for prevalent osteoporosis among women, respectively, while the same significant association was not observed among men (All $P > 0.05$). In addition, the positive association between osteoporosis and SBP, MAP, and PP was observed among postmenopausal women but not among per-menopausal women, the ORs were 1.10 (1.04,1.15), 1.16 (1.08,1.25), and 1.12 (1.04,1.20), respectively.

Discussion

Focused on rural population, this large cross-sectional study is the first research which aimed to explore the association between different blood pressure proxies and osteoporosis, and to detect the potential gender-difference. In rural China, the prevalence of osteoporosis was 14.07% for men and 22.64% for women and the significantly positive association between hypertension and osteoporosis was observed in women but not in men. Each 10 mmHg increase in SBP and PP corresponded with 1.07-fold (1.03,1.12)

and 1.08-fold (1.02,1.15) risk for prevalent osteoporosis among women, respectively. This positive association was still significant among non-hypertension women and postmenopausal women, but not exist among pre-menopausal women and men, which hinted that the gender-difference association between blood pressure and osteoporosis may attribute to the menopause status.

The prevalence of osteoporosis in China varied across researches, but it is consistent that women were more prone to suffer osteoporosis in all researches [4]. For instance, a Chinese research completed in northern China reported that the prevalence of osteoporosis was 19.8% among elderly men and 36.9% among elderly women. While in northwestern China, the reported prevalence of osteoporosis was 8.08% among elderly men and 9.65% among elderly women [21]. One nationwide research reported that the prevalence of osteoporosis was 6.46% among men and 29.13% among women [5]. Another nationwide research reported that the prevalence of osteoporosis was 13.5% for men and 29.0% for women [3]. While in this research, the prevalence of osteoporosis was 14.07% for men and 22.64% for women in Chinese rural areas. The difference in prevalence of osteoporosis may be attributed to the different measurements of BMD across researches.

Numerous researches have repeatedly linked hypertension with prevalent osteoporosis [22]. Early cohort study conducted in 3676 elderly white women found increasing SBP corresponded with increasing rate of bone loss ($P_{\text{non-linear}}$ <0.05) [10], which was similar to our results. Recent cross-section study also indicated that both SBP and DBP were inversely related with BMD of proximal femoral and lumbar vertebral, the betas were − 0.382, -0.290 and − 0.340 of SBP, and − 0.318, -0.340, and − 0.304 of DBP [23]. Similar association was also observed in Chinese population [24–25]. Conducted in Tibet, a retrospective cross-sectional study also found SBP was inversely associated with BMD T-score of spine and femoral neck or hip among diabetic postmenopausal women [24]. Recent case-control study also indicated that hypertension was positively associated with osteoporosis [26]. In contract to our results, Javed et al. reported that hypertension was not correlated with low BMD at either lumbar spine or both femoral necks among African American females aged over 65 years [27]. A retrospective analysis also pronounced that there was no significant difference between hypertension and non-hypertension participants in BMD of femur or spinal [28]. Evidence from Korea National Health and Nutrition indicated that lumbar spine osteoporosis was not significantly associated with blood pressure [29]. A population-based Mendelian randomization study conducted in European population also revealed a potential positive association between PP and forearm BMD [30]. These differences may be the results of different regions, environment exposures, lifestyles, races and other underlying factors.

Gender-difference association between blood pressure with osteoporosis was repeatedly observed in previous researches. For instance, Loke et al. observed that both SBP and DBP were negatively associated with BMD among women, but not significantly associated among Men [25]. A recent longitudinal study also highlighted that BMD of femoral neck was lower in women with hypertension than those without hypertension (0.80 *vs.* 0.82), while in men, hypertension was positive associated with BMD of lumbar spine and femoral neck [13]. Additionally, evidence from a meta-analysis pronounced that the association between fracture and hypertension was slightly stronger in women (pooled OR = 1.52,

95% CI 1.30–1.79) than in men (pooled OR = 1.35, 95% CI 1.26–1.44) [12]. Given the positive association between blood pressure and osteoporosis was disappeared in pre-menopausal women, the gender-difference association may be attributed to the menopause status. Additionally, lower sample size in men may also contribute to this statistical insignificance.

Despite the potential mechanism of blood pressure and osteoporosis was not yet clarified, limited researches still provided various evidence. Calcium may be a primarily bridge between blood pressure and osteoporosis [31]. Previous researches have reported that participants with hypertension had a higher calcium elimination and a lower intestinal absorption than non-hypertension participants, which contributed to a lower calcium concentration in the plasma [13, 31–32]. To sustain a suitable blood calcium level, bones may breakdown and bring calcium into the blood [33]. Therefore, bone may be porous and prone to fractures [31, 34–35]. In addition, recent research also found hypertension corresponded with the low level of 25-hydroxy vitamin D and osteocalcin, which leaded to a low bone turnover [11]. During menopause and postmenopause, the reduced estrogen in women would contribute to an increased osteoclastic resorption activity without a suitable increase in osteoblastic activity, which lead to a net loss of bone and a decreased bone strength [36–38]. Thus, the low bone strength of may explain the significant association between blood pressure and osteoporosis was only observed among postmenopausal women but not among men or pre-menopausal women.

To the best of our knowledge, this is the first research to explore the gender-difference associations between divergent blood pressure proxies and osteoporosis among rural population. Despite large sample population and appropriate statistical methods could make this research more convincing, some limitations should be noted. Firstly, only 7689 participants from Henan Rural Cohort study were included in this research and missing information may induce inevitable errors. Secondly, quantitative ultrasound (QUS) measures might underestimate osteoporosis prevalence, however, it appeared capable of replacing dual X-ray considering its portability and low-cost in the large-scale study. Thirdly, we did not examine vitamin D, osteoprotegerin, osteocalcin levels of the subjects. These metabolic makers might help to enrich our results. Fourthly, lack of the information of anti-hypertensive drags would weaken the results. Moreover, the unraveling reverse causality cannot be ruled out because of the survey based on a cross-sectional study.

In conclusion, hypertension and high blood pressure were positive associated with prevalent osteoporosis among women in rural areas. This positive association was still significant in non-hypertension women but not in pre-menopausal women, which hinted that this gender-difference association may be attributed to menopause status. These findings might hopefully identify that divergent blood pressure proxies may be the potential indicators for screening high osteoporosis risk among women in rural areas with limited medical resource. And more attention should be attention to the postmenopause women with high blood pressure.

Statements And Declarations

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Competing Interests

Xianhong Yi, Huiling Tian, Xinwei Chen, Ning Kang, Xiaotian Liu, Chongjian Wang, and Jun Pan declare that they have no conflict of interest.

Author contributions

JP and CW conceived and designed the study. XY and HT analyzed and interpreted the data. XY, HT and XC drafted the manuscript. NK and XL provided technical direction and writing assistance in the preparation of this manuscript. All authors critically revised the manuscript and approved the final version for publication.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Zhengzhou University Life Science Ethics Committee (Code: [2015] MEC (S128)), and all the participants provided informed consent.

Clinical Trail Registration

The Henan Rural Cohort Study has been registered at Chinese Clinical Trial Register (Registration number: ChiCTR-OOC-15006699). http://www.chictr.org.cn/showproj.aspx?proj=11375

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors affirm that human research participants provided informed consent for publication.

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39. **Statements and Declarations**

Figures

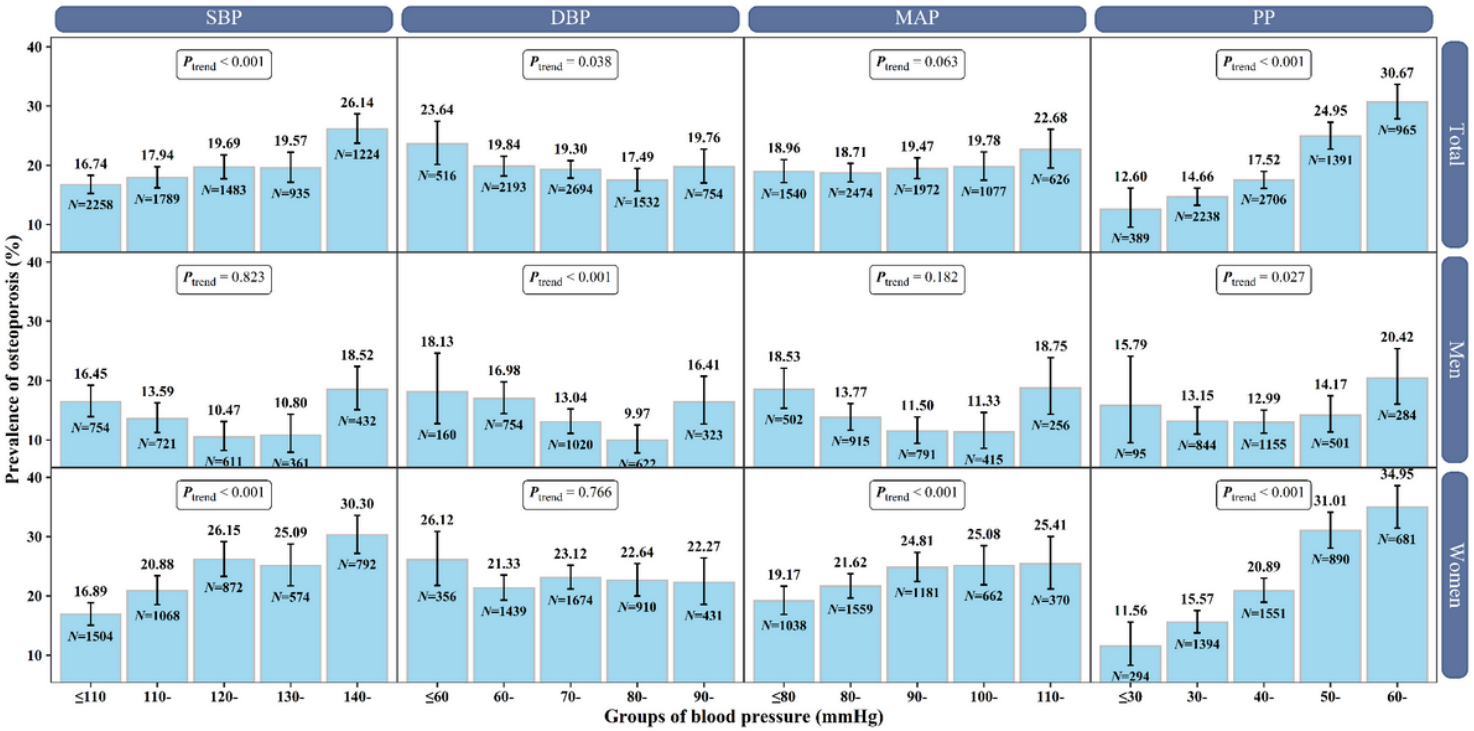

Figure 1

The prevalence of osteoporosis in different blood pressure group by gender. The prevalence of osteoporosis in different blood pressure group by gender. Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; HTN: hypertension

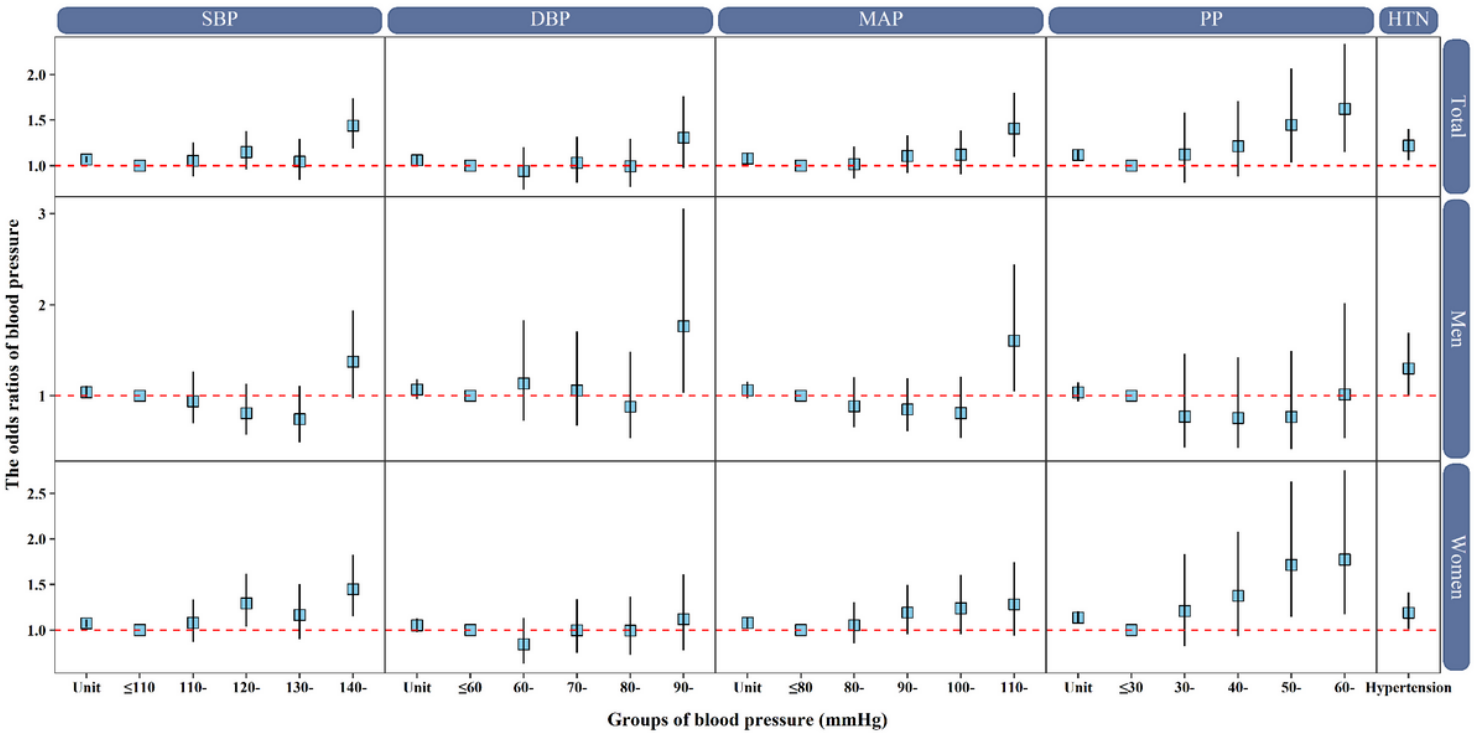

Figure 2

Gender-difference association between blood pressure and osteoporosis. Model was adjusted by age, gender, educational level, marital status, average monthly income, smoking, drinking status activity, high-fat diet, fruits and vegetables intake, and BMI; the reference group was ≤110 mmhg in SBP, ≤60 mmhg in DBP, ≤80 mmHg in MAP, ≤30 mmHg in PP, and non-hypertension in HTN; unit means each 10 mmHg increase in blood pressure. Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; HTN: hypertension.

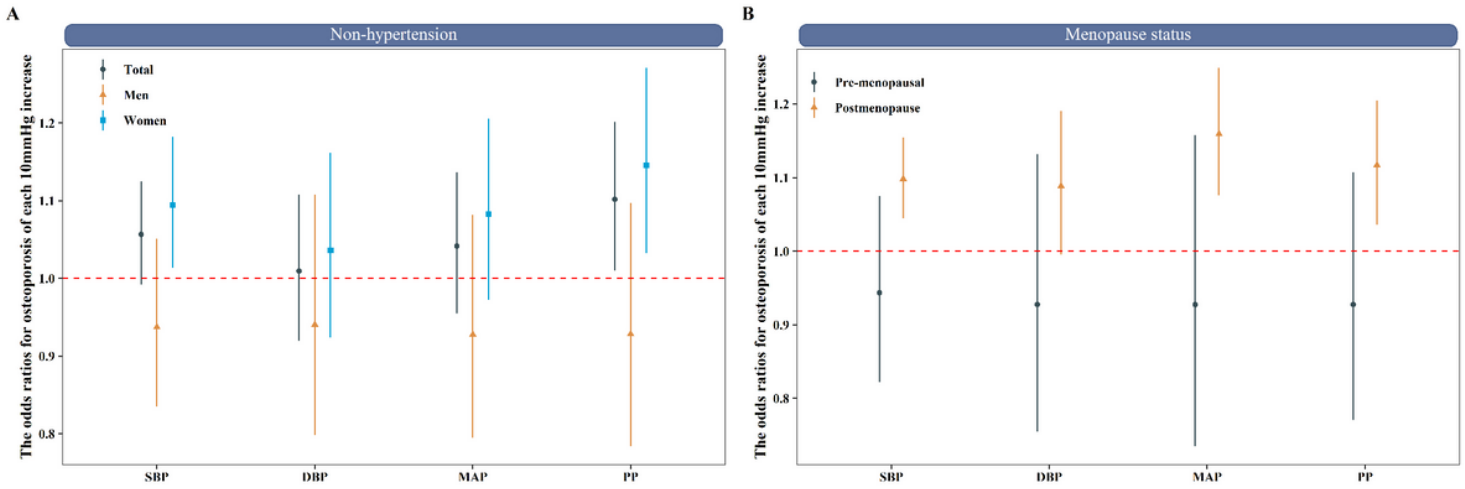

Figure 3

The association between each 10 mmHg increase in blood pressure and osteoporosis among non-hypertension participant (A) and women by menopause status (B). Adjusted by age, gender, educational level, marital status, average monthly income, smoking, drinking status activity, high-fat diet, fruits and vegetables intake, and BMI. Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure.

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