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ORIGINAL ARTICLE

Association between hypertension and fragility fracture: a longitudinal study

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Abstract
Summary Hypertension is an independent risk factor for osteoporosis and osteoporotic fracture in postmenopausal women.
Introduction Although hypertension has been suggested to be associated with increased fracture risk, it is not clear whether the association is independent of bone mineral density (BMD). The present study sought to examine the interrelationships between hypertension, BMD, and fracture risk.
Methods The study included 1,032 men and 1,701 women aged 50 years and older who were participants in the Dubbo Osteoporosis Epidemiology Study. BMD at the femoral neck and lumbar spine was measured by dual energy X-ray absorptiometry (GE-LUNAR Corp., Madison, WI, USA). The presence of hypertension was ascertained by direct interview and verification through clinical history. The incidence of fragility fractures was ascertained by X-ray report during the follow-up period (1989–2008). The Cox proportional hazards model was used to assess the association between hypertension and fracture risk.
Results Women with hypertension had lower BMD at the femoral neck (0.79 versus 0.82 g/cm^2, P=0.02) than those without the disease. After adjusting for BMD and covariates, hypertension was an independent risk factor for fragility fracture [hazard ratio (HR), 1.49; 95 % CI, 1.13–1.96]. In men, hypertension was associated with higher femoral neck BMD (0.94 versus 0.92 g/cm^2, P=0.02), but the association between hypertension and fracture risk did not reach statistical significance.
Conclusion Hypertension is associated with increased fracture risk in women, and the association is independent of BMD.

Keywords Bone mineral density · Fracture risk · Hypertension · Osteoporosis

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Introduction

Hypertension, osteoporosis, and osteoporotic fracture are highly prevalent among elderly populations. The conditions could lead to many serious clinical consequences, including premature mortality. The worldwide prevalence of hypertension in adults ranges from 20 % to 40 % [1, 2]. Hypertension is a major risk factor for ischemic heart diseases, renal failure, and other cardiovascular diseases [3–5]. Hypertension accounts for 4.5 % of all diseases and 1~4 % of all deaths [2, 6]. Moreover, osteoporosis has increasingly become a major public health problem in the elderly population because it affects approximately 25 % of women and 10 % of men aged 60 years and older [7–9]. The residual lifetime risk of fracture

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is approximately 44 % in women and 25 % in men from the age of 60 years [9]. Hip fracture, a serious consequence of osteoporosis, is associated with an increased risk of death. Among hip fracture patients, approximately 50 % have long-term disability, 25 % require long-term nursing home care, and 18 % die within the first year after the fracture [10].

Hypertension and osteoporosis share some etiologies and genetic links. Advancing age, menopause, and physical inactivity are risk factors of both hypertension and osteoporosis [11, 12]. Animal and human studies have reported that high blood pressure is associated with abnormalities of calcium metabolism, leading to increased urinary calcium loss [13–15]. Those abnormalities due to hypertension may eventually be responsible for higher bone loss [16] and lower bone mineral density (BMD) [2, 17].

Recent studies have suggested that hypertension is a risk factor for fracture risk [18–20]. Low BMD is a major risk factor for fracture. However, it is not clear whether the hypertension–fracture association is independent of BMD. To have a better understanding of the relationship between hypertension and fracture risk, we therefore undertook a population-based cohort study to evaluate the interrelationships between hypertension, BMD, and fracture risk.

Study design and methods

Study participants

The study participants were drawn from the ongoing Dubbo Osteoporosis Epidemiology Study (DOES), which was initiated in mid-1989, and had subsequently followed biennially. The study was approved by the St. Vincent's Campus Research Ethics Committee, and written informed consent was obtained from all participants. The age and sex distribution of the Dubbo population closely resembled the Australian general population [21]. Participants were excluded from the analysis if they (a) were less than 50 years of age, (b) had fracture at same year or 1 year prior to the diagnosis of hypertension, (c) had Paget's or other bone-related diseases, and (d) used anti-hypertension treatment in non-hypertension group (Fig. 1). In total, 2,733 participants (1,032 men and 1,701 women) were included in the analysis.

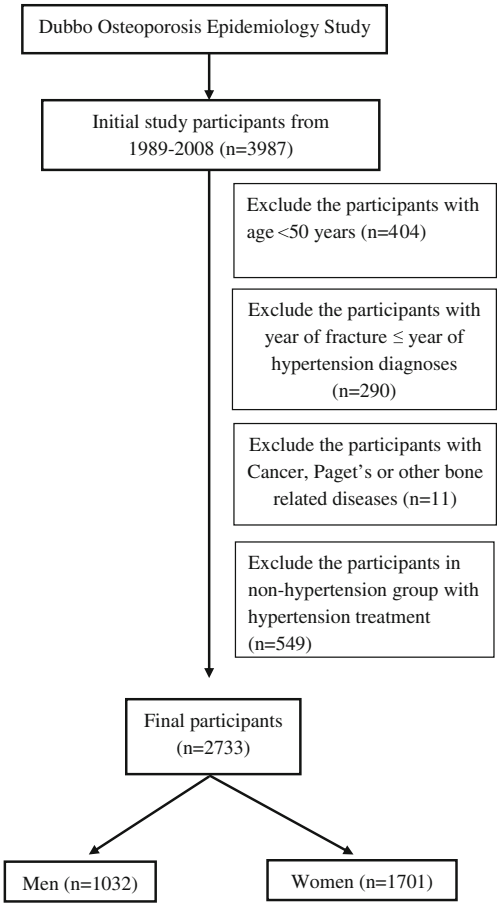

Fig. 1 Flowchart of the participants excluded from the study

Assessment of risk factors

At baseline, participants were interviewed by a nurse coordinator who administered a structured questionnaire to obtain anthropometric data (e.g., age, weight, and height) and other lifestyle factors (e.g., smoking, physical activity, and dietary calcium intake). Weight was measured (to the nearest 0.1 kg) on an electronic scale. Height, without shoes, was measured to the nearest 0.1 cm by a wall-mounted stadiometer. Smoking was defined as any past or present use of tobacco. Physical activity was estimated by the Framingham questionnaire, which includes five levels of daily activities: basal, sedentary, light, moderate, and heavy activity [22]. Dietary calcium intake was assessed based on a food frequency questionnaire [23]. The number of falls during the past 12 months was also recorded. Cardiovascular medications including beta-blockers, thiazide diuretics, non-thiazide diuretics, and other related medications were ascertained through direct interview and medication record. Systolic blood pressure and diastolic blood pressure (millimeter of mercury) were measured at baseline visit, and subsequent visits for some, but not all participants.

BMD (grams per centimeter) at the femoral neck and lumbar spine was measured by dual energy X-ray absorptiometry (GE-LUNAR Corp., Madison, WI, USA). The coefficient of reliability of BMD measurement was 0.96 and 0.98 at the proximal femur and lumbar spine, respectively [24].

Ascertainment of fracture

Low trauma and non-pathological fracture were ascertained from X-ray reports which were obtained from the two, or at times three, radiology services from 1989 [25]. Fractures were included only if the report of fracture was definite and, on

review, had occurred with low trauma (e.g., fall from standing height or less). Fractures clearly due to major trauma (such as motor vehicle accidents), or those due to underlying diseases (such as cancer or bone-related disease), or those of digits, skull, or cervical spine were excluded from the analysis. We did not assess morphometric vertebral fracture. All types of fragility fracture were classified into three main groups: any fracture (at all sites), hip fracture, and clinical vertebral fracture. Prior fracture was defined as any fragility fracture that had occurred before the initial visit.

Ascertainment of hypertension and cardiovascular diseases

The presence of hypertension was ascertained by direct interview and verification through clinical history. The ascertainment of hypertension was further validated based on the agreement of illness code (e.g., 500) and illness comments (e.g., hypertension or high blood pressure) from direct interview or medical records. Cardiovascular diseases (CVDs) including heart failure, stroke, myocardial infarction, ischemic heart disease, and atherosclerosis were ascertained via the similar protocol as hypertension with each participant. We excluded participants with hypertension or CVDs ascertained at the same year or after an incidence of fracture.

Data analysis

The univariate association between hypertension and fracture risk was assessed by a series of Kaplan–Meier curves, in which the time-to-fracture was shown for individuals with and without hypertension. The Cox's proportional hazards model was used to assess the association between hypertension and fracture risk, with adjustment for potential covariates such as age, femoral neck BMD, body weight, body height, smoking, physical activity, dietary calcium intake, falls, prior fracture, and cardiovascular diseases. The association between blood pressure and fracture risk was examined in a subgroup of participants whose data on blood pressure were available. The association between hypertension and BMD was analyzed by the multiple linear regression model, with covariates being age, body weight, body height, smoking, physical activity, and dietary calcium intake. All analyses were performed using the Statistical Analysis System (version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and incidence of fracture

At baseline, 21 % (n=220) of men and 25 % (n=420) of women had hypertension (Table 1). Individuals with hypertension were significantly older, had lower dietary calcium intake, and higher prevalence of CVDs and cardiovascular medications than those without hypertension. In addition, women with hypertension had lower body height, higher BMI, lower femoral neck BMD, and lower physical activity levels than those without hypertension. The incidence of any fragility fracture was higher in the hypertensive participants than in the non-hypertensives in men (19 % versus 12 %) and women (32 % versus 22 %).

In the univariate analysis, advancing age, lower body weight, as well as body height, BMI, BMD, falls, and prior fracture were each associated with increased fracture risk in both genders (Table 2). Smoking history and lower calcium intake were each associated with higher fracture in men but not in women.

Hypertension and bone mineral density

In women, femoral neck BMD were lower in women with hypertension than those without hypertension (0.80 vs. 0.82 g/cm^2, P=0.001; Fig. 2). After adjusting for covariates, the association between hypertension and femoral neck BMD in women was still significant (P=0.02). However, in men, hypertension was associated with higher lumbar spine BMD (P=0.047) and higher femoral neck BMD (P=0.02).

Hypertension and fracture risk

The overall cumulative incidence of any fracture, hip fracture, and clinical vertebral fracture for men with hypertension was 16.3, 3.3, and 5.7 per 1,000 person-years compared with 11.3, 2.8, and 4.5 per 1,000 person-years for those without hypertension, respectively. In women, the overall cumulative incidence of fracture was also higher in the hypertensive group than in the non-hypertension group (27.6 vs. 21.6 per 1,000 person-years for any fracture; 5.7 vs. 1.1 per 1,000 person-years for hip fracture, and 9.3 vs. 8.8 per 1,000 person-years for vertebral fracture). In women, cumulative incidence of any hip fracture was much higher in the hypertensive group than in the non-hypertension group (Fig. 3).

A key confounder between hypertension and any fracture was cardiovascular medications. Among those cardiovascular medications, beta-blockers [HR, 0.60 (0.42–0.86)] and other cardiovascular related medications [HR, 0.46 (0.36–0.59)], but not thiazide [HR, 0.87 (0.60–1.26)] or non-thiazide diuretics [HR, 0.94 (0.73–1.22)], were significantly associated with reduced fracture risk than in the multiple adjusted model. In men, the association between hypertension and fracture risk did not reach statistical significance.

After adjusting for the confounder in the multivariable Cox's proportional hazards models, hypertension was a significant independent risk factor for any fragility fracture in women with HR being 1.49 (95 % CI, 1.13–1.96), but not in men (HR, 1.53; 95 % CI, 0.94–2.48). Although hypertension was associated with increased risks of hip fracture and vertebral fracture, the magnitude of association did not reach statistical significance (Table 3).

Table 1 Baseline characteristics of participants stratified by hypertension and gender (n=2,733)

	Men (n=1,032)			Women (n=1,701)		
	Hypertension	Non-hypertension	P value	Hypertension	Non-hypertension	P value
N (%)	220 (21 %)	812 (79 %)		420 (25 %)	1,281 (75 %)	
Age (years)	70 (6)	68 (7)	0.012	70 (7)	68 (8)	<0.001
Weight (kg)	82 (12)	81 (14)	0.310	68 (14)	67 (14)	0.093
Height (cm)	173 (6)	174 (7)	0.316	160 (6)	161 (6)	0.008
BMI (kg/m^2)	27 (4)	27 (4)	0.078	27 (5)	26 (5)	0.004
Lumbar spine BMD (g/cm^2)	1.281 (0.210)	1.249 (0.212)	0.047	1.056 (0.196)	1.058 (0.198)	0.821
Femoral neck BMD (g/cm^2)	0.944 (0.149)	0.923 (0.147)	0.063	0.793 (0.134)	0.818 (0.139)	0.001
Physical activity (METs)	33 (5)	33 (6)	0.072	30 (3)	31 (3)	<0.001
Dietary calcium intake (mg/day)[a]	538 (363, 759)	664 (456, 921)	<0.001	540 (373, 754)	693 (483, 933)	<0.001
Falls (n, %)	40 (18 %)	124 (15 %)	0.295	118 (28 %)	326 (25 %)	0.284
Smokers (n, %)	140 (64 %)	477 (59 %)	0.189	107 (25 %)	380 (30 %)	0.099
Prior fracture (n, %)	7 (3 %)	53 (7 %)	0.060	28 (7 %)	113 (9 %)	0.165
Cardiovascular diseases	75 (34 %)	162 (20 %)	<0.001	108 (26 %)	140 (11 %)	<0.001
Cardiovascular medications (n, %)	206 (94 %)	283 (35 %)	<0.001	407 (97 %)	486 (38 %)	<0.001
Incidence of						
Any fractures (n, %)	41 (18.6 %)	95 (11.7 %)	0.007	135 (32.1 %)	283 (22.1 %)	<0.001
Hip fractures (n, %)	9 (4.1 %)	25 (3.1 %)	0.456	32 (7.6 %)	55 (4.3 %)	0.007
Vertebral fractures (n, %)	15 (6.8 %)	40 (4.9 %)	0.268	52 (12.4 %)	124 (9.7 %)	0.115

Values are means (SD), unless otherwise specified

METs metabolic equivalents

[a] Median (Q1, Q3)

Table 2 Association between risk factors and fracture for men and women: univariate analysis (n=2,733)

Variables	Per unit[a]	Men[b]			Women[b]		
		Any fracture	Hip fracture	Vertebral fracture	Any fracture	Hip fracture	Vertebral fracture
Age (years)	7	1.75 (1.47, 2.08)	2.47 (1.75, 3.49)	1.75 (1.34, 2.30)	1.46 (1.33, 1.60)	2.22 (1.85, 2.67)	1.53 (1.33, 1.75)
Weight (kg)	−12	1.34 (1.13, 1.59)	1.62 (1.13, 2.32)	1.63 (1.23, 2.16)	1.28 (1.16, 1.41)	2.26 (1.75, 2.92)	1.34 (1.15, 1.57)
Height (cm)	−6	1.22 (1.06, 1.42)	1.31 (0.98, 1.77)	1.36 (1.08, 1.73)	1.15 (1.05, 1.26)	1.47 (1.21, 1.79)	1.17 (1.02, 1.35)
BMI (kg/m^2)	−4	1.25 (1.03, 1.51)	1.53 (1.02, 2.29)	1.46 (1.07, 2.01)	1.21 (1.10, 1.32)	1.82 (1.44, 2.30)	1.24 (1.08, 1.43)
LSBMD (g/cm^2)	−0.2	1.54 (1.29, 1.83)	1.88 (1.33, 2.67)	2.05 (1.55, 2.71)	1.76 (1.57, 1.97)	1.95 (1.51, 2.51)	2.32 (1.94, 2.79)
FNBMD (g/cm^2)	−0.14	1.94 (1.62, 2.32)	3.55 (2.47, 5.10)	2.48 (1.87, 3.29)	1.92 (1.72, 2.15)	3.79 (2.94, 4.89)	1.97 (1.66, 2.35)
PA (METs)	−3	1.01 (0.92, 1.11)	0.98 (0.82, 1.17)	1.10 (0.93, 1.29)	1.08 (0.97, 1.19)	1.57 (1.18, 2.10)	1.08 (0.92, 1.26)
DCI (mg/day)	−300	1.23 (1.04, 1.46)	1.76 (1.18, 2.63)	1.18 (0.91, 1.53)	1.00 (0.92, 1.08)	1.03 (0.87, 1.23)	0.92 (0.82, 1.03)
Falls	Y/N	3.29 (2.33, 4.65)	1.39 (0.63, 3.08)	1.89 (1.06, 3.39)	5.75 (3.91, 5.78)	3.37 (2.20, 5.16)	2.77 (2.06, 3.72)
Smokers	Y/N	1.49 (1.03, 2.14)	0.94 (0.48, 1.87)	4.64 (2.10, 10.3)	1.11 (0.90, 1.37)	1.10 (0.70, 1.73)	1.11 (0.81, 1.53)
Prior fracture	Y/N	1.13 (0.53, 2.42)	2.91 (1.02, 8.28)	1.16 (0.36, 3.72)	2.11 (1.57, 2.84)	2.31 (1.28, 4.17)	1.40 (0.84, 2.35)
CVDs	Y/N	0.86 (0.57, 1.29)	1.29 (0.62, 2.69)	1.07 (0.58, 1.96)	0.90 (0.69, 1.17)	1.27 (0.75, 2.16)	0.90 (0.60, 1.35)
Cardiovascular medications	Y/N	0.99 (0.70, 1.38)	1.05 (0.54, 2.05)	1.23 (0.85, 1.78)	0.76 (0.62, 0.92)	0.94 (0.56, 1.60)	0.97 (0.79, 1.20)

BMI body mass index, *LSBMD* lumbar spine bone mineral density, *FNBMD* femoral neck bone mineral density, *PA* physical activity, *DCI* dietary calcium intake, *CVDs* cardiovascular diseases, *METs* metabolic equivalents

[a] Values are approximately 1 SD

[b] Values are hazard ratios (95 % confidence interval)

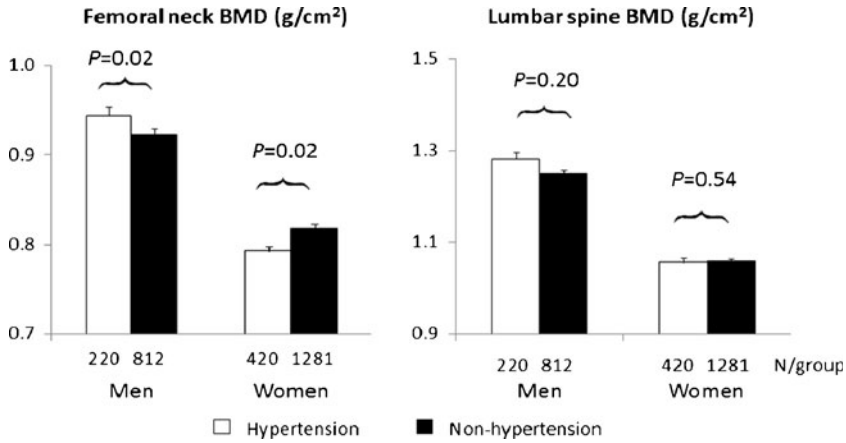

Fig. 2 Femoral neck BMD and lumbar spine BMD for hypertensive versus non-hypertensive participants for men and women. *P* values were adjusted for age, body weight, body height, smoking, physical activity, dietary calcium intake, prior fracture, cardiovascular diseases, and cardiovascular medications

Table 3 Association between hypertension and fracture risk in men and women: results of multivariate analysis (n=2,733)

Fracture	Men	Women
Any fracture	1.53 (0.94, 2.48)	1.49 (1.13, 1.96)
Hip fracture	1.16 (0.44, 3.08)	1.48 (0.84, 2.60)
Vertebral fracture	1.67 (0.76, 3.66)	1.12 (0.74, 1.70)

[a] Adjusted for age, femoral neck BMD, body weight, body height, smoking, physical activity, dietary calcium intake, falls, prior fracture, cardiovascular diseases, and cardiovascular medications. Values are hazard ratios (95 % confidence interval)

In unadjusted models, blood pressure was not significantly related to fracture risk. However, after adjusting for confounders and medications, each SD higher in systolic blood pressure was associated with a 22 % greater risk of hip fracture in women (HR, 1.22; 95 % CI, 1.00–1.47), but not in men (HR, 0.88; 95 % CI, 0.62–1.24).

Discussion

Hypertension has been postulated as a risk factor for fracture, but it is not clear whether the association is independent of BMD. In this large-scale population-based cohort study, we have shown that hypertension is associated with reduced femoral neck BMD and increased fracture risk in women. More importantly, the association between hypertension and fracture was independent BMD. In men, the association between hypertension and fracture risk had similar pattern as in women but did not reach statistical significance. These findings suggest that controlling high blood pressure may have beneficial effect on bone health in women, and possibly in men.

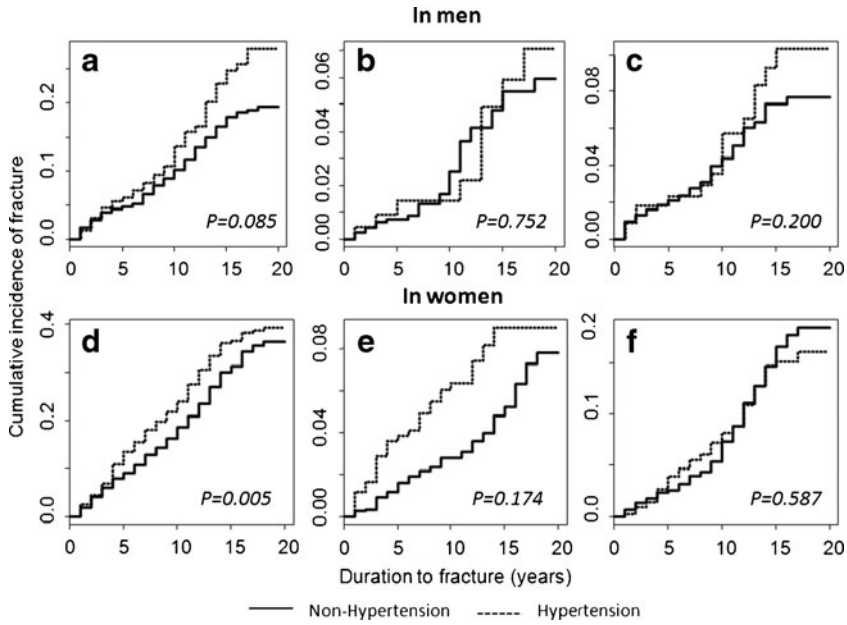

Fig. 3 Kaplan–Meier estimates for incidence of fractures stratified by hypertension and gender. In men: (**a**) any fracture, (**b**) hip fracture, and (**c**) vertebral fracture. In women: (**d**) any fracture, (**e**) hip fracture, and (**f**) vertebral fracture. *P* value was adjusted for age, femoral neck BMD, body weight, body height, smoking, physical activity, dietary calcium intake, prior fracture, falls, cardiovascular diseases, and cardiovascular medications

Our results extend previous findings in a case–control study [18] which suggested that a diagnosis of hypertension was a risk factor for fracture. In addition, our findings are consistent with another case–control study, in which hypertension was associated with a 50 % greater risk of hip fracture in women but not in men [20]. The non-significant association between hypertension and fracture in men was likely due to small number of fractures in the study.

The association between hypertension and osteoporosis has biological basis. High blood pressure is associated with increased loss of calcium in the urine, leading to a negative calcium balance of bone remodeling [15, 26, 27]. Indeed, an epidemiological study found increased loss rate of mineral from the skeleton with increasing blood pressure [16]. Moreover, hypertension is related to high levels of parathyroid hormone, which accelerate bone turnover, decreasing bone mass, and decreasing bone quality [28]. Finally, high blood pressure may insidiously damage brain structures related to gait control and balance [29], and this could predispose to falls and subsequent fracture [30]. Although we have mentioned several potential mechanisms of hypertension on bone fragility and fracture, other mechanisms may be present and these need to be further evaluated.

Regardless of the mechanisms involved, the present study's findings have several implications at the population level because hypertension and osteoporosis are highly prevalent in the elderly population. Between 20 % and 40 % of the elderly population have hypertension [31]. Similar to hypertension, osteoporosis is also high prevalent, affecting between 20 % and 30 % postmenopausal women worldwide [32]. Considering the two conditions together, around 61 % participants with osteoporosis also have hypertension [33]. Given those two closely interrelated medical conditions, these results suggest that properly controlled blood pressure may potentially benefit bone health and protect against fragility fracture.

A major strength of our study is large sample size and population-based cohort design. Moreover, all fracture cases in our present study were well validated and closely monitored over a mean of 10 years of follow-up. The study also considered the most important confounders such as age, BMD, and CVDs, which allow us to have a more precise and reliable estimate of association. However, a weakness of this study is that we could not ascertain the severity of hypertension. Also, some diagnoses of hypertension in the control group may have been missed during follow-up period. To minimize this possibility, we have excluded individuals in the non-hypertension group with hypertension medications. The participants in the study were mainly Caucasian; therefore, the results cannot be generalized to other ethnicities. The number of hip fractures and vertebral fractures in men was relatively low, and the finding in men could be suffered from type II error.

In summary, in this large population-based cohort study, women with hypertension had lower femoral neck BMD and higher risk of fracture than those without hypertension. Given the high prevalence of osteoporosis and hypertension in the general population, this finding raises the possibility that antihypertensive agents may materially protect against fragility fractures in the countries with high incidence of hypertension, such as the USA, Europe, and Japan. Moreover, if this effect and effect size are confirmed, hypertension should be considered a risk factor for osteoporosis and should be used for fracture prediction and prevention. These finding would be extremely important for those with hypertension and a high risk of fracture.

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Conflicts of interest None.

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