

# Low bone mineral density is associated with increased arterial stiffness in participants of a health records based study

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**Aims:** Many epidemiological studies have shown that low bone mineral density (BMD) and atherosclerosis appear to be related. However, their precise correlation is not completely understood after full adjustment the shared confounders of atherosclerosis and bone metabolism. The aim of this cross-sectional study was to investigate the relationship between BMD and subclinical atherosclerosis in a healthy Chinese population and the difference in gender.

**Methods:** The study population consisted of 2,487 subjects (1,467 men, 1,020 women) who participated in health check-up programs and were selected to be free of major diseases which might affect atherosclerosis and bone metabolism. Bone status was assessed by BMD in lumbar spine. The brachial-ankle PWV (baPWV) was assessed as a functional marker of atherosclerosis. The ankle-brachial index (ABI), carotid artery intima-media thickness (CIMT), estimated glomerular filtration rate (eGFR) and microalbuminuria were evaluated as indexes of structural markers of atherosclerosis.

**Results:** After adjustment for risk factors, significant association was shown between baPWV and BMD in both genders (male:  $r=-0.084$ ,  $P=0.035$ ; female:  $r=-0.088$ ,  $P=0.014$ ). The correlation was stronger in females than in males, and in females, the correlation was stronger after menopause. Similarly, mean baPWV differed significantly according to the decreased BMD (normal BMD, Osteopenia, Osteoporosis). In contrast, no significant differences were observed for ABI, CIMT, eGFR or microalbuminuria with BMD.

**Conclusions:** Independent of confounding factors, low BMD is associated with the functional marker of subclinical atherosclerosis (increased baPWV), but not with structural markers (ABI, CIMT, eGFR or microalbuminuria) among healthy females and males.

**Keywords:** Low bone mineral density (BMD); atherosclerosis; health check-up; arterial stiffness

Submitted Mar 05, 2015. Accepted for publication Apr 10, 2015.

doi: 10.3978/j.issn.2072-1439.2015.04.47

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.04.47>

## Introduction

Osteoporosis is a substantial worldwide public health issue (1). As a metabolic disorder, osteoporosis characterized low bone mass and bone microarchitectural deterioration. Atherosclerosis is a chronic disease characterized by thickening and losses of elasticity in the walls of arteries and exhibits a high rate of morbidity and mortality due to

strokes, cardiovascular and peripheral vascular diseases (2). Recently, compelling evidence has suggested a direct, age-independent association between these two degenerative disorders (3-5). Lower bone mass and rapid bone loss are associated with an increased risk of developing atherosclerosis.

There are several measures of assessing subclinical atherosclerosis. The brachial-ankle PWV (baPWV)

is a simple and non-invasive method to assess arterial stiffness and is known to be an independent predictor for cardiovascular events (6). The ankle-brachial index (ABI) is initially a simple measure of the severity of lower-extremity peripheral arterial disease (PAD). Later, it was shown that the ABI is an indicator of atherosclerosis at other vascular sites (7). Carotid artery intima-media thickness (CIMT) is a surrogate marker of generalized atherosclerosis and correlated with coronary artery disease and stroke (8). Renal dysfunction and albuminuria could be as new cardiovascular risk factors. Both estimated glomerular filtration rate (eGFR) and microalbuminuria share a common association with atherosclerosis, which may be explained in part by inflammation, metabolic abnormality of calcium and phosphorus, endothelial damage or dysfunction (9-11).

Several studies have evaluated the relationship between low bone mineral density (BMD) and some of the measures of subclinical atherosclerosis. However, most of the studies examined the relationship without adjusting risk factors of atherosclerosis and bone metabolism. And the study population are most of postmenopausal women with hypertension, diabetes or other cardiovascular diseases (12-14). So the apparent relationship may be distorted by the effects of these confounders. In addition, only a few studies have explored this association in the Asian population, and even they have reported conflicting results (15-17).

In the present study, we sought to improve upon these previous investigations in two ways. First, we examined the relationship between low BMD and atherosclerosis in healthy Chinese people from health check-up programs. The study subjects included both men and female, and also both premenopausal and postmenopausal women. Second, we extended the previous studies by examining baPWV, ABI, CIMT, eGRF and microalbuminuria; this expanded investigation allowed us to evaluate the overall measures of subclinical atherosclerosis with BMD.

## Materials and methods

### Study population

Study subjects comprised 5,837 consecutive individuals who visited the Third Xiangya Hospital of Central South University for health check-up programs including BMD measurement between 2012 and 2013. Subjects consisted of inhabitants of a mixed urban/rural area. Exclusion criteria are the participants who are known to be suffering from any major diseases which might affect atherosclerosis

and bone metabolism, such as hypertension, diabetes mellitus, hyperlipidaemia, obesity, osteomalacia, history of osteoporotic fractures and so on. And taking medications with established effects on bone turnover (including vit D, calcium, corticosteroids, bisphosphonates and sex hormones) were also excluded. Consequently, 2,487 healthy participants were included in the analysis. The subjects selection diagram is described in *Figure 1*. Informed written consent was obtained from all of the participants and the study protocol was approved by the Ethics Guidelines Committee of the Central South University.

Hypertension was defined to be present in subjects with a history of hypertension who were taking anti-hypertensive drugs. Hyperlipidaemia was diagnosed in subjects with serum total cholesterol (TC) levels  $\geq 6.22$  mmol/L and/or triglyceride (TG) level  $\geq 2.26$  mmol/L and/or low-density lipoprotein cholesterol (LDL-C) level  $\geq 4.14$  mmol/L, or in subjects with history of cholesterol lowering therapy. Diabetic state was diagnosed in patients with fasting plasma glucose level  $\geq 7.1$  mmol/L and/or random plasma glucose level  $\geq 11.1$  mmol/L, or history of anti-diabetic therapy. In addition, the presence of obesity is regarded as body mass index (BMI)  $\geq 28$  kg/m<sup>2</sup>.

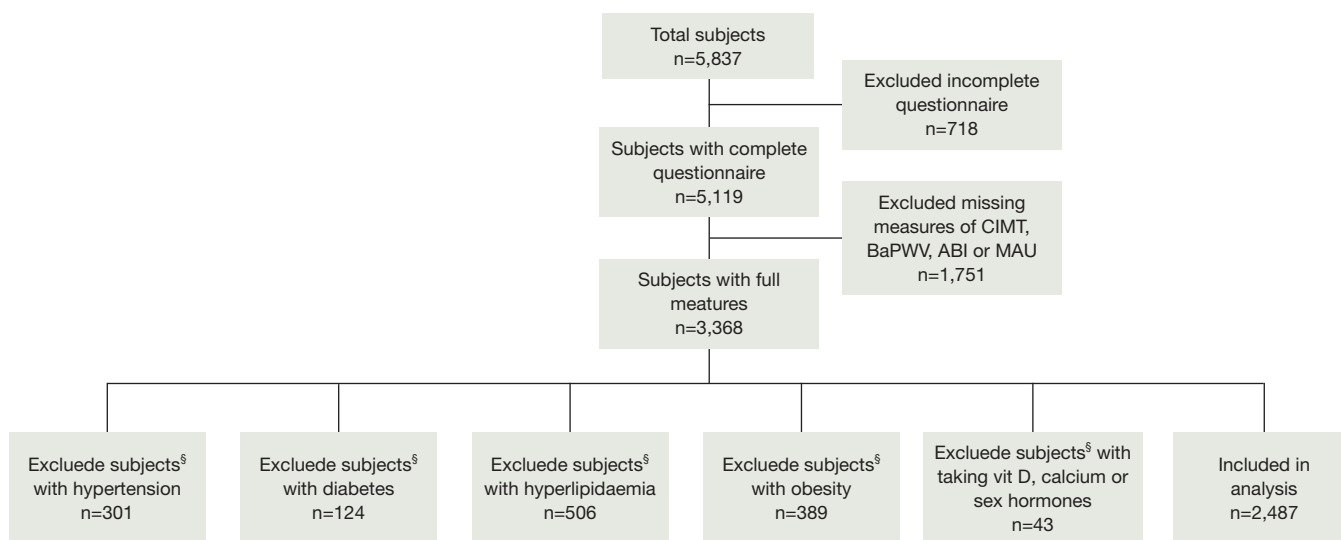
### Clinical measurements

All participants underwent a routine clinical examination and a detailed questionnaire. Age, sex, height, weight, current medications from pill bottles, previous medical diagnoses, exercise, smoking history and alcohol consumption were recorded.

The term smokers included subjects who smoking  $>1$  cigarette per day and last over 6 months. The alcohol consumption was defined as those who take beer, wine (including Chinese wine) or liquor at least two days per week and last over 12 months. The standard for exercise was physical activity for 30 min or longer and more than 3 times per week. BMI was calculated as body weight in kilograms divided by the square of body height in meters. Blood pressure (BP) was measured on the right upper arm in the sitting position after 10-15 min of seated rest using a validated digital automatic BP monitor.

### Measurement of lumbar spine BMD

The lumbar spine BMD was measured at the lumbar spine L1-L4 by dual-energy X-ray absorptiometry (DXA) with a Lunar prodigy densitometer (Discovery A, Hologic, USA).



**Figure 1** Flow chart describing the subjects selection procedure. <sup>§</sup>, the subjects have a certain degree of overlap.

The results were interpreted in terms of BMD ( $\text{g}/\text{cm}^2$ ). According to the World Health Organization's criteria, the participants were categorized into the normal BMD (T-score at  $-1.0$  and above), osteopenia (T-score between  $-1.0$  and  $-2.5$ ), or osteoporosis (T-score at or below  $-2.5$ ) groups (18). Daily quality control was carried out by the measurement of a Lunar phantom. To avoid inter-observer variability, all DXA measurements were performed by a well-trained technician who was blinded to subjects' characteristics. The correlation coefficient of intraobserver reproducibility was 96.4%.

#### Measurement of baPWV and ABI

The baPWV and ABI were simultaneously measured with an automatic waveform analyser (Colin Co., Komaki, Japan). Briefly, after having taken at least a 5-min rest in the supine position, the subjects attached cuffs around their upper arms and ankles. The baPWVs were recorded and calculated using the formula  $(L_a - L_b) / \Delta T_{ba}$ , in which  $L_a$  is the distance from the heart to the ankle;  $L_b$  the distance from the heart to the brachium; and  $\Delta T_{ba}$  the transmission time between the brachial and posterior tibial artery waveforms. ABI was measured as the ratio of the ankle systolic BP divided by the arm systolic BP. The average baPWV and ABI from the left and right sides were used for the analysis. Two trained technicians performed the measurements of baPWV and ABI, and the inter-observer and intra-observer coefficients of variation were 4.9% and

7.8%, respectively.

#### Measurement of CIMT

Measurements of CIMT were performed on a common carotid artery and evaluated using a Siemens Acuson Sequoia™ 512 Ultrasound System (Mountain View, CA, USA) with a 10 MHz linear array transducer with the subjects in the supine position. The CIMT was identified as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo, which was measured at three different sites on the left and right sides (the far wall of the common carotid artery, approximately 1.5 cm to proximal to the carotid bulb, as well as at sites 0.5 cm upstream and downstream, free from plaques) on the longitudinal views. We calculated the bilateral mean and then the average of both sides, using a total of six measurements per subject. Two experienced ultrasonography technicians conducted all of the ultrasound examinations. The correlation coefficients for inter- and intra-observer variability were 7.9% and 9.6%, respectively.

#### Laboratory measurements

Morning blood and urine samples were collected after at least 12 h of overnight fasting. Several chemical parameters such as fasting blood glucose (FBG), TC, TG, high-density lipoprotein cholesterol (HDL-C), LDL-C, serum creatinine (Scr), blood urea nitrogen (BUN) and serum uric acid

(SUA) levels were obtained by standard enzymatic methods. Glomerular filtration rate (GFR) was estimated using the modified MDRD equation for the Chinese population (19). Microalbuminuria concentrations in our reference range (0-30 mg/dL) were evaluated by the immunoturbidimetry method.

### Statistical analysis

There was a large gender difference in the BMD; therefore all analyses were stratified by sex. Statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Percent and means with standard deviations of variables were calculated for descriptive statistics. Multivariable linear regression models were applied to evaluate the association between BMD and variables of atherosclerosis, using BMD as the dependent variable and the ABI, baPWV, CIMT, eGFR and microalbuminuria as independent variables, respectively. Associations were adjusted for sets of covariates in two models. Model 1 adjusted for age. Model 2 adjusted additionally for body mass index, systolic BP, diastolic BP, TG, HDL-C, LDL-C, FBG, cigarette smoking (former + current), alcohol consumption (former + current), exercise and menopausal status (female only). Because the formula of eGFR referred to age and SCr, the parameter of age not included in the multivariate linear regression analysis to avoid confusing linearity within the regression model when eGFR was the independent variable. Multi-collinearity was not detected during screening for tolerance values of less than 0.15 for all variables in the fully adjusted models.

Pearson's correlation coefficient analyses were used to examine the relationship between the values of BMD and the values of baPWV. Mean baPWV by BMD stratified (normal BMD, osteopenia and osteoporosis) were tested by analysis of covariance first after adjustment for age and then after full adjustments. Values of  $P < 0.05$  were considered statistically significant.

## Results

### Clinical characteristics of the study participants

The sex-specific characteristics of 1,467 male and 1,020 female participants are shown in *Table 1*. The average age of men was 45.72 years, and the average age of women was 44.71 years. For both men and women, the means of BMI, SBP, DBP, TG, TC, LDL-C, HDL-C and FBG were

within normal range. All other variables were significantly lower in women than in men except exercise, HDL-C, eGFR and BMD is higher ( $P < 0.05$ ).

### Associations between BMD and variables of subclinical atherosclerosis

*Table 2* displays the results of multiple linear regression analysis of variables of subclinical atherosclerosis, used to evaluate their association with the BMD. The baPWV was significantly associated with BMD in both male and female after adjusting for age only (model 1) (male:  $\beta = -0.079$ ,  $P = 0.006$ ; female:  $\beta = -0.121$ ,  $P < 0.001$ ). When adjusted for other covariates (model 2), significantly associations persisted in both sexes (male:  $\beta = -0.064$ ,  $P = 0.035$ ; female:  $\beta = -0.088$ ,  $P = 0.014$ ). The other variables of subclinical atherosclerosis (ABI, CIMT, eGFR or microalbuminuria) failed to reach statistical significance with the BMD.

### Correlations of BMD with baPWV

We detected that baPWV was an independent factor significantly with BMD. Pearson's correlation was used to identify the BMD associated with the change in baPWV. *Figure 2* shows baPWV significantly correlated with BMD in both genders. The correlation was stronger in females than in males (male:  $r = -0.013$ ,  $P < 0.001$ ; female:  $r = -0.36$ ,  $P < 0.001$ ). In females, the correlation was stronger in post-menopause than pre-menopause (pre-menopause:  $r = -0.13$ ,  $P < 0.001$ ; post-menopause:  $r = -0.35$ ,  $P < 0.001$ ).

### Comparison of mean baPWV according to the decrease in BMD

*Table 3* lists the mean values ( $\pm$  SE) for baPWV according to the BMD classified as different groups (normal BMD, Osteopenia, Osteoporosis). The mean baPWV values differed significantly by the decrease in BMD and these differences remained significant after we adjusted for other covariates in both sexes (male: 1,310.85, 1,320.18, and 1,342.93 cm/s, respectively ( $P = 0.029$ ); female: 1,216.34, 1,231.57, and 1,269.11 cm/s, respectively ( $P = 0.039$ )).

## Discussion

The present study has several strengths. First, the study population is represented by a comparatively large sample size and was highly selected to exclude hypertension,

**Table 1** Characteristics of participants distributed by gender

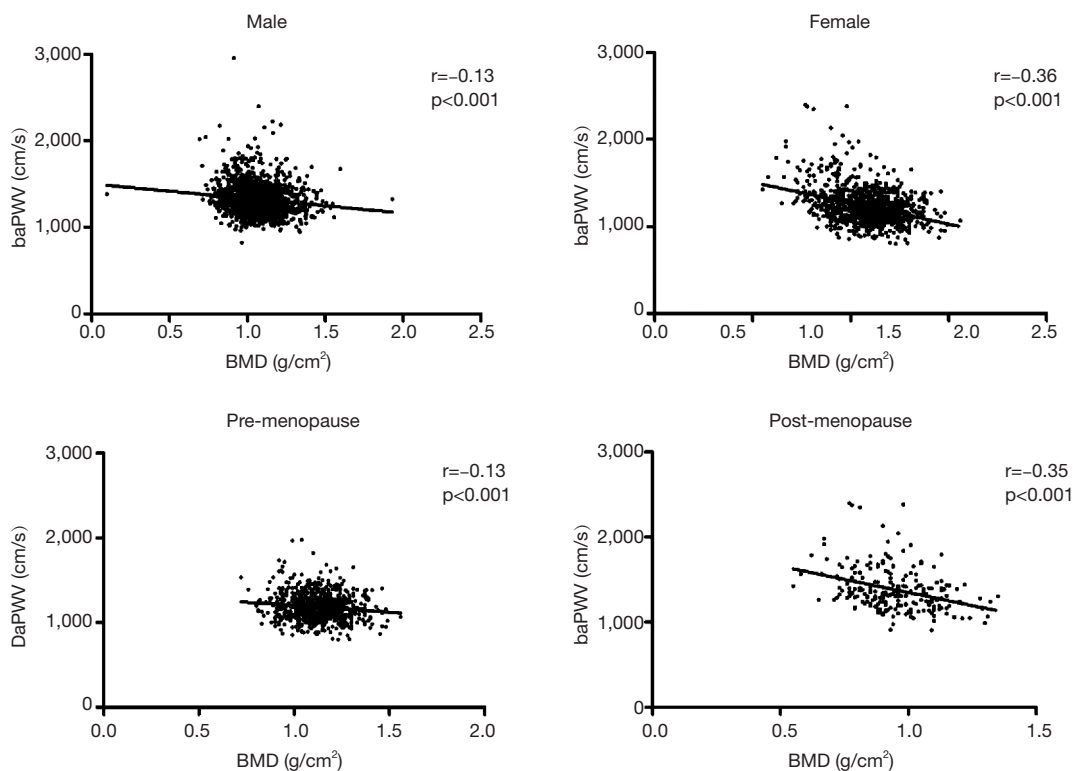
Characteristics	Male (n=1,467)	Female (n=1,020)	P value
Age (years)	45.72±8.38	44.71±8.51	0.004
BMI (kg/m <sup>2</sup> )	23.94±2.38	22.04±2.37	<0.001
Systolic BP (mmHg)	121.68±10.98	112.72±12.81	<0.001
Diastolic BP (mmHg)	77.19±8.48	71.42±8.91	<0.001
TC (mmol/L)	4.74±0.71	4.66±0.71	<0.001
LDL cholesterol (mmol/L)	2.67±0.64	2.40±0.63	0.005
TGs (mmol/L)	1.37±0.44	1.04±0.40	<0.001
HDL cholesterol (mmol/L)	1.45±0.32	1.78±0.37	<0.001
Fasting glucose (mmol/L)	5.01±0.59	4.92±0.51	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	128.70±23.46	141.07±27.06	<0.001
Microalbuminuria (mg/L)	20.41±38.60	17.00±35.16	0.025
BaPWV (cm/s)	1,321.10±175.88	1,226.11±200.35	<0.001
ABI	1.12±0.07	1.08±0.07	<0.001
CIMT (mm)	0.69±0.07	0.65±0.07	<0.001
BMD (L1-L4) (g/cm <sup>2</sup> )	1.07±0.14	1.09±0.15	<0.001
No. of subjects with: (%)			
Cigarette smoking	832 (56.71)	37 (3.63)	<0.001
Alcohol consumption	803 (54.73)	253 (24.80)	<0.001
Exercise	327 (22.29)	273 (26.76)	0.010
Menopausal status		221 (21.67)	

BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; BMD, bone mineral density; CIMT, carotid intima-media thickness.

**Table 2** Multiple linear regression models to test variables with Lumbar spine BMD

Independent variable	Adjustment model	Male		Female	
		Standardised coefficients (β)	P value	Standardised coefficients (β)	P value
baPWV (cm/s)	Model 1	-0.079	0.006	-0.121	<0.001
	Model 2	-0.064	0.035	-0.088	0.014
ABI	Model 1	0.050	0.061	0.030	0.304
	Model 2	0.030	0.251	0.019	0.498
CIMT (mm)	Model 1	0.015	0.606	-0.032	0.295
	Model 2	-0.012	0.675	-0.041	0.154
eGFR (mL/min/1.73 m <sup>2</sup> )	Model 1	-0.006	0.826	-0.037	0.199
	Model 2	-0.001	0.979	-0.013	0.646
Microalbuminuria (mg/L)	Model 1	-0.040	0.119	0.021	0.436
	Model 2	-0.027	0.296	0.026	0.322

Model 1, adjusted for age; Model 2, adjusted for the following: age, sex, cigarette smoking, alcohol consumption, exercise, menopausal status (female), BMI, systolic blood pressure, diastolic blood pressure, TG, HDL-C, LDL-C, fasting glucose. Categorical variables (sex, cigarette smoking, alcohol consumption, exercise, menopausal status) were used as dummy variable, therefore assigned values of 1 (yes) and 0 (no), respectively. BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.



**Figure 2** Relationship between baPWV and BMD in male, female, pre- and post-menopausal women. baPWV, brachial-ankle PWV; BMD, bone mineral density.

**Table 3** Comparison means of baPWV according to sex-specific of normal BMD, osteopenia, osteoporosis

BMD	Mean baPWV (mean ± SD) (cm/s)			
	Male		Female	
	Model 1	Model 2	Model 1	Model 2
Normal	1,307.87±7.45	1,310.85±7.03	1,212.00±6.92	1,216.34±6.64
Osteopenia	1,319.27±5.64	1,320.18±5.35	1,237.15±8.88	1,231.57±8.37
Osteoporosis	1,348.43±9.43	1,342.93±9.68	1,276.6±19.11	1,269.11±18.90
P	0.009	0.029	0.004	0.039

Model 1 and Model 2 adjusted for same confounders listed in *Table 2*. BMD, bone mineral density.

diabetes mellitus, hyperlipidaemia, and cardiovascular disease as confounders to interfere with the credibility of the results. Second, cardiovascular risk factors as exercise, cigarette smoking, alcohol consumption and menopausal status are well characterized. Third, we explored the comprehensive measurements of subclinical atherosclerosis with BMD. To our knowledge, this is the first study to evaluate at the same time baPWV as a functional marker (sclerosis), ABI, CIMT, eGRF and microalbuminuria as structural markers (atherosis) in relation to BMD in a

healthy population. Additionally, our study extends these findings to men and also the middle-aged group.

Our data demonstrate that, decreased BMD is significantly associated with baPWV in both genders, but not with ABI, CIMT, eGRF and microalbuminuria. After adjustment was made for several confounding factors, the relationship is weakened, but remained significant. The results indicated that the association was both age- and traditional cardiovascular risk-independent. As in this study, previous studies showed an association between BMD and

baPWV mainly in women (16,17,20,21). Two Japanese studies found that lumbar spine BMD was associated with baPWV in postmenopausal women (16,20). A Korean study found an association between lumbar spine BMD and baPWV only in women, and no association between femur BMD and baPWV in both genders (21). Another Korean study found an association between total hip BMD and baPWV in women (17). However, there are some controversial results (22,23). In a study of 385 Chinese individuals, Liang *et al.* detected no association between total hip BMD and lumbar spine BMD with baPWV in both women and men (22). The above studies may have been limited by the sample size or the inability to adjust for many proposed confounding factors.

Although the correlation between BMD and baPWV was significant in both genders, it was weaker in men, raising the possibility of a sex-differential association. In women, the correlation was stronger after menopause. This may explain why estrogen might play a unique role in regulating the calcification of the bones and atherosclerosis. Bones and arteries are all target tissues for estrogen. Estrogen receptors have been identified on osteoclasts, osteoblasts, endothelial and smooth muscle cells in the arterial wall, indicating that estrogen has a direct effect on the bones and arteries (24). Estrogen also down-regulates the pro-inflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ . This increased state of pro-inflammatory cytokine activity is able to accelerate postmenopausal bone mineral loss and to change vascular homeostasis to favour the development of atherosclerosis (25). In addition, the lack of estrogens induces a decrease in osteoprotegerin (OPG), which may play an important role in the mechanisms of bone loss and atherogenesis (26). The changes in the action of estrogen deficiency would make the relationship between baPWV and BMD more conspicuous in females, especially in postmenopausal women.

The previous investigations gave little evidence for a correlation between ABI and BMD (15,22). But several studies have reported that a low bone density is associated with peripheral artery disease (PAD) (27,28). The patients with PAD were more likely to have osteoporosis or increased fracture risk. Therefore, the association between ABI and BMD could probably be observed in the stage of clinical atherosclerosis, rather than in any preclinical status, especially in healthy people free of cardiovascular diseases in our study.

Few studies have found an association between CIMT and BMD (22,23,29). Shaffer *et al.* reported decreased

BMD is correlated with increased CIMT in older (>60 years of age) (30). de Almeida Pereira Coutinho *et al.* found a significant association between CIMT and BMD in men with type 2 Diabetes (31). In addition, some researchers detected that the presence of carotid plaque was associated with bone mineral loss (12,29). These findings indicated that the association between CIMT and BMD may be age- and cardiovascular risk factor-dependent or that it might be seen in relatively late-stage atherosclerosis, such as carotid plaque formation.

To our knowledge, this is the first study used eGFR and microalbuminuria as measures of subclinical atherosclerosis to investigate the association with BMD. The eGFR and microalbuminuria are surrogate markers that assess the cardiovascular subclinical organ damage. Recently, several reports have been noted that decreased eGFR and increased microalbuminuria were associated with atherosclerosis (10,11). The atherosclerotic process, especially in small vessels within the glomerular basement membrane may modify glomerular barrier permeability, thus leading to the excretion of albumin into the urine and the decreased eGFR. In our study, microalbuminuria and eGFR were not associated with BMD in both men and women. This result may be explained by the healthy subjects who were enrolled in our study, as their eGFR and microalbuminuria values were in the normal range, making the correlation not significant. The patients with chronic renal dysfunction (eGFR <60 mL/min per 1.73 m<sup>2</sup>) may disturb extracellular calcium and phosphorous metabolic to the bones, resulting in bone loss and extensive vascular calcification.

The exact mechanism behind the association between BMD and arterial stiffness is not completely understood. There are several potential mechanisms to explain this link. Both osteoporosis and atherosclerosis share similar or common risk factors. Bone-associated matrix proteins, homocysteine, high levels of OPG, inflammatory mediators, estrogen and vitamin D deficiency all play an important role both in bone metabolism and in the development of atherosclerosis (32). In addition, osteoporosis and cardiovascular diseases may share common genetic bases (33). Still, this claim needs to be clarified in the future research.

Atherosclerosis consists two distinguished process: one is structural process (atherosis) caused by lipid infiltration in cells and extracellularly, and the other is functional process (sclerosis) caused by connective tissue deposition and by functional disturbance of the endothelium, leading to reduced arterial compliance (34). In our study, the

relationship exists between functional marker (baPWV) and BMD. Of note, however, is that no significant association was observed between structural markers (ABI, CIMT, eGRF or Microalbuminuria) and BMD. Therefore, we suppose that the association between atherosclerosis and BMD would be more prone to be conducted in the process of functional disturbance.

This study possesses some limitations. First, the BMD measured in the study was only at the lumbar spine, a single bone site. It was possible that degenerative conditions (osteophytosis and endplate sclerosis) contributed to increased lumbar spine BMD, potentially weakening the relationship between BMD and atherosclerosis. Second, in order to represent of healthy subjects, we used the factitious exclusion method to select the study population, which could introduce bias. Third, we did not measure bone metabolism regulators, such as OPG, osteopontin (OPN) and matrix Gla protein (MGP) levels, which could present possible mechanisms for the link between BMD and atherosclerosis. Finally, this is a cross-sectional design of this study. Therefore, no conclusions on causes or consequences can be made.

## Conclusions

In conclusion, our results showed that decreased BMD is correlated with increased baPWV among healthy females and males, independent from any confounding factors. We suggest that lower BMD may be associated with arterial stiffness and a higher risk of cardiovascular disease. Therefore, we need to pay adequate attention to populations with lower BMD, to provide effective non-pharmacological and pharmacological interventions and to conduct further evaluations on vascular disease, especially in post-menopausal women.

## Acknowledgements

*Funding:* Supported by Foundation of Hunan Provincial Science & Technology Department (2014SK3062); Supported by Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-year Plan of China (2013BAI04B01).

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** Wang YQ, Yang PT, Yuan H, Cao X, Zhu XL, Xu G, Mo ZH, Chen ZH. Low bone mineral density is associated with increased arterial stiffness in participants of a health records based study. *J Thorac Dis* 2015;7(5):790-798. doi: 10.3978/j.issn.2072-1439.2015.04.47