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Arterial Stiffening Relates to Arterial Calcification But Not to Noncalcified Atheroma in Women

A Twin Study

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Objectives Our aim was to examine the relationship of arterial stiffness to measures of atherosclerosis, arterial calcification, and bone mineral density (BMD); the heritability of these measures; and the degree to which they are explained by common genetic influences.

Background Arterial stiffening relates to arterial calcification, but this association could result from coexistent atherosclerosis. A reciprocal relationship between arterial stiffening/calcification and BMD could explain the association between cardiovascular morbidity and osteoporosis.

Methods We examined, in 900 women from the Twins UK cohort, the relationship of carotid-femoral pulse wave velocity (cfPWV) to measures of atherosclerosis (carotid intima-media thickening; carotid/femoral plaque), calcification (calcified plaque [CP]; aortic calcification by computed tomography, performed in subsample of 40 age-matched women with low and high cfPWV), and BMD.

Results The cfPWV independently correlated with CP but not with intima-media thickness or noncalcified plaque. Total aortic calcium, determined by computed tomography, was significantly greater in subjects with high cfPWV (median Agatston score 450.4 compared with 63.2 arbitrary units in subjects with low cfPWV, $p = 0.001$). There was no independent association between cfPWV and BMD. Adjusted heritability estimates of cfPWV and CP were 0.38 (95% confidence interval: 0.19 to 0.59) and 0.61 (95% confidence interval: 0.04 to 0.83), respectively. Shared genetic factors accounted for 92% of the observed correlation (0.38) between cfPWV and CP.

Conclusions These results suggest that the association between increased arterial stiffness and the propensity of the arterial wall to calcify is explained by a common genetic etiology and is independent of noncalcified atheromatous plaque and independent of BMD. (J Am Coll Cardiol 2011;57:1480–6) © 2011 by the American College of Cardiology Foundation

Stiffening of large elastic arteries is a hallmark of vascular aging strongly predictive of cardiovascular disease (CVD) related events such as myocardial infarction and stroke (1). Animal models and observations in humans suggest that arterial calcification might be an important determinant of arterial stiffness (2–4). It has been suggested that vascular calcification might occur in parallel with demineralization of bone, with a reciprocal relationship between arterial stiffening and osteoporosis explaining the epidemiological association of osteoporosis with CVD events (5–8). However, whether the association of arterial stiffening with arterial calcification merely reflects the presence of atherosclerosis is unknown (9), and the relation of arterial stiffness to bone mineral density (BMD) has not been clearly established. The object of the present study was to examine the relationship of arterial stiffness to measures of atherosclerosis, arterial calcification, and BMD in women of middle age from the Twins UK cohort. We examined the heritability of these characteristics and the degree to which they could be explained by common genetic influences.

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Methods

Subjects. Subjects were female Caucasian twins (n = 900, 396 monozygotic [MZ] and 504 dizygotic [DZ]) from the Twins UK cohort, a cohort with characteristics similar to the general U.K. population (10). All women underwent assessment of arterial stiffness by measurement of carotid-femoral pulse wave velocity (cfPWV), carotid/femoral ultrasound, and BMD. A subsample of 40 age-matched women selected from the first (low cfPWV) and third tertile (high cfPWV) of the cfPWV distribution underwent computed tomography (CT) of the aorta. The study was approved by St. Thomas' Hospital Research Ethics Committee, and written informed consent was obtained from all subjects.

Biochemistry. Fasting serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, calcium, and phosphate were measured in an accredited laboratory. Low-density lipoprotein cholesterol was estimated with the Friedewald equation. In the CT substudy, serum 25 (OH) vitamin D; C-terminal telopeptides of type 1 collagen, as a marker of bone resorption; and bone-specific alkaline phosphatase and osteocalcin, as a marker of bone formation, were measured by chemiluminescence and by enzyme-linked immunosorbent assays (IDS, Boldon, United Kingdom).

Blood pressure and pulse wave velocity (PWV). Measurements were performed in a quiet temperature-controlled vascular laboratory (22°C to 24°C). Brachial blood pressure was measured in duplicate, with a validated oscillometric device (Omron 705CP, Omron, Tokyo, Japan) after subjects had been seated for at least 10 min. The cfPWV was obtained with subjects supine with the SphygmoCor system (Atcor Medical, Sydney, Australia). The path distance between the carotid and femoral sites was estimated from the distance between the sternal notch and femoral artery at the point of applanation.

Carotid intima-media thickness (IMT) and carotid/femoral plaque. The left and right carotid and femoral arteries were visualized with B-mode ultrasound (Siemens CV70, Siemens, Erlangen, Germany, with 13-MHz vascular probe). Common carotid IMT was measured in the near and far walls, 1 to 2 cm proximal to the carotid bifurcation with automated wall tracking software (Medical Imaging Applications, Coralville, Iowa) during diastole in an area free of overt plaque. Mean values of IMT in the near and far walls of both arteries were used for analysis. Arterial walls were examined for plaque in the common carotids, carotid bifurcations, origins of the internal and external carotid arteries, common femoral arteries, femoral bifurcations, and the origins of the superficial and deep femoral arteries. Plaque was defined in the longitudinal view as focal widening and protrusion into the lumen of ≥1.5-mm thickness relative to neighboring areas and confirmed in transverse view. Plaque was graded according to echogenicity into predominately echolucent/noncalcified (>50% of similar echogenicity to blood) or echogenic/calcified (>50% of similar echogenicity to the bright echo of the media–adventitia interface) (11,12). Measurements were made by 2 experienced observers (B.J. and M.C.) unaware of clinical data of the study participants at the time of measurement.

BMD. The BMD was determined at the lumbar spine (L1 to L2) and hip with dual X-ray absorption (Hologic Discovery, Hologic, Bedford, Massachusetts). Quality control scans were performed daily with a spine phantom.

CT. Non–contrast-enhanced CT was performed with a 16-slice CT helical scanner (Brilliance CT component of the Philips Precedence SPECT/CT system, Philips, Eindhoven, the Netherlands). Three-millimeter transverse nonoverlapping slices between the carotid and aortic bifurcation were acquired (16 × 1.5 mm collimation, 120 kVp, 55 mAs/slice, 0.5-s gantry rotation time) and viewed offline with a Hermes workstation. A modification of the Agatston score was used to quantify aortic calcium: each cross-sectional slice was analyzed separately, and calcification was defined as any area >1 mm^2 with attenuation ≥130 Hounsfield units. The Agatston score (13) for each such area was determined by multiplying lesion area (total number of pixels) by a weighting factor (of 1, 2, 3, and 4 for maximum attenuations of 130 to 199, 200 to 299, 300 to 399, and >400 Hounsfield units, respectively). Calcium was further quantified in cubic millimeters with the volume score calculated as the product of voxel volume and number of voxels in the region of interest. For both methods, the total calcium score was obtained by summing the score in each cross-sectional slice.

Statistical analysis. Data analysis was performed with SPSS (version 16.0, SPSS, Inc., Chicago, Illinois) and STATA software (version 6, Stata Corporation, College Station, Texas). Subject characteristics are presented as mean ± SD unless otherwise stated. Comparisons between groups were made with Student *t* test, Wilcoxon signed rank test, chi-square test, and analysis of variance (Bonferroni test was used for post hoc comparison). Univariate regression analysis was first used to examine the relationships of vascular measures to age, mean arterial pressure (MAP), heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, current smoking, and menopausal status and treatment for blood pressure, cholesterol, diabetes, and osteoporosis. Forward stepwise multivariable regression

Abbreviations and Acronyms

ACE = additive genetic component (a^2), common (c^2), and unique (e^2 incorporating measurement error) environment components

BMD = bone mineral density

cfPWV = carotid-femoral pulse wave velocity

CI = confidence interval

CP = calcified plaque

CT = computed tomography

CVD = cardiovascular disease

DZ = dizygotic twins

IMT = intima-media thickness

MAP = mean arterial pressure

MZ = monozygotic twins

PWV = pulse wave velocity

analysis including all variables significantly associated on univariate analysis was then performed to examine independent associations. Correlation of observations between twin pairs was adjusted for with a cluster mean or, in multiple regression analysis, a cluster variable (14). All statistical tests were done at the 5% level of significance.

Heritability analysis. Heritability analysis was performed with the classic twin model (15). Intraclass correlation coefficients were compared for MZ and DZ twins to examine twin resemblance. Variance of each phenotype was assumed to derive from an additive genetic component (a^2), common (c^2), and unique (e^2; incorporating measurement error) environment components (ACE model). Structural equation modeling was used to estimate parameters of the ACE model and corresponding confidence intervals (CIs) with the method of maximum likelihood (Mx software, University of Virginia). Significance of each parameter was determined by likelihood ratio tests. Significantly skewed variables were log transformed for analysis. Heritability of categorical variables was estimated with a liability-threshold model. Thresholds and the tetrachoric correlation were estimated with the method of maximum likelihood. Variance decomposition of the correlation in liability was applied to an ACE model. For age adjustment, the liability threshold was assumed to be linearly related to age (16). A common genetic basis for the association between arterial characteristics was explored by examining cross-trait, cross-twin correlations in a bivariate model (17). The phenotypic correlation (r_{ph}) between cfPWV (categorized into 3 groups divided at the 75th and 90th percentiles) and calcified plaque (CP) was partitioned into that explained by additive genetic factors (r_a), shared environment (r_c), and nonshared environment (r_e).

Results

Subject characteristics. Characteristics of women in the total cohort are shown in Table 1. The MZ and DZ twins were comparable for age, blood pressure, and cfPWV. There were small but statistically significant differences in smoking, antihypertensive treatment, low-density lipoprotein cholesterol, and glucose between MZ and DZ twins (Table 1). Of the subjects, 41% had plaque present at 1 or more of the arterial sites. Of these, 32% were classified as echolucent (noncalcified) plaques, and 68% were classified as echogenic (calcified) plaques.

Relation of cfPWV to risk factors, IMT, and carotid/femoral plaque. In univariate analysis, cfPWV was associated with most traditional risk factors, including age, blood pressure, low-density lipoprotein-cholesterol, triglycerides, and fasting glucose. However, in multivariable analysis, cfPWV was significantly, independently, positively correlated only with age, blood pressure, heart rate, and fasting glucose (each $p < 0.0001$) (Table 2). The cfPWV was not independently correlated to carotid IMT when this was added to a multivariable model (including age, MAP, heart rate, glucose, or a model including all variables significantly correlated with cfPWV on univariate analysis). There was also no independent correlation between cfPWV and IMT when subjects taking antihypertensive treatment were excluded. Similarly, cfPWV was not independently correlated with the presence of noncalcified plaque. However, cfPWV was significantly correlated with the presence of CP ($p = 0.01$, adjusting for all confounders, including hormone replacement therapy and menopausal status) (Table 2). Presence of CP remained significantly associated with PWV after adjustment for twin family structure ($p < 0.05$). The cfPWV was significantly higher in subjects with CP versus those with no plaque (mean 9.69 ± 1.9 m/s vs. 8.54 ± 1.4 m/s, respectively, $p < 0.01$, and those with noncalcified plaque, 9.08 ± 1.7 m/s, $p < 0.01$). The difference in PWV remained significant between individuals with no plaque and CP after adjustment for age, MAP, heart rate, fasting glucose, hormone replacement therapy use, and menopausal status.

Table 1 Characteristics of MZ and DZ Twins in the Total Cohort

	MZ (n = 396)	DZ (n = 504)
Age (yrs)	57.7 ± 10.0	58.0 ± 8.0
Height (cm)	161.4 ± 6.0	161.9 ± 6.0
Weight (kg)	69 ± 13	69.7 ± 13.0
Current smokers	27 (7)	60 (12)*
Post-menopausal	247 (62)	316 (63)
Diabetes	6 (2)	3 (1)
Systolic blood pressure (mm Hg)	127.4 ± 17.0	128.6 ± 15.0
Diastolic blood pressure (mm Hg)	78.2 ± 10.0	78.9 ± 9.0
Heart rate (beats/min)	63.5 ± 9.0	63.2 ± 9.0
Total cholesterol (mmol/l)	5.71 ± 1.1	5.57 ± 0.9
HDL cholesterol (mmol/l)	1.77 ± 0.5	1.82 ± 0.5
LDL cholesterol (mmol/l)	3.42 ± 1.0	3.24 ± 0.9†
Triglycerides (mmol/l)	1.14 ± 0.6	1.12 ± 0.6
Glucose (mmol/l)	5.15 ± 0.6	5.05 ± 0.6
Hypertension treatment	94 (24)	81 (16)†
Lipid-lowering treatment	51 (13)	65 (13)
HRT treatment	22 (6)	37 (7)
cfPWV (m/s)	8.98 ± 1.8	8.89 ± 1.6
CIMT (mm)	0.66	0.66
Plaque	150 (38)	217 (43)
Echolucent	46 (12)	71 (14)
Echogenic	104 (26)	146 (29)
BMD (hip, g/cm^2)	0.91 (0.13)	0.91 (0.12)
BMD (lumbar spine, g/cm^2)	0.98 (0.14)	0.96 (0.14)

Data are mean ± SD or n (%). Compared with monozygotic (MZ) twins, *$p < 0.01$; †$p < 0.05$.
BMD = bone mineral density; cfPWV = carotid-femoral pulse wave velocity; CIMT = common carotid intima-media thickness; DZ = dizygotic; HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein.

CT. Women that underwent a CT scan had characteristics similar to those in the main study, and there were no significant differences in age, MAP, heart rate, fasting glucose, or bone chemistry between women selected from the first and third tertiles of the distribution of cfPWV in the main study (Table 3). The mean PWV for subjects selected from the first tertile was similar to that for the

Table 2 Multiple Regression Model: Relation of cfPWV to Risk Factors and Measures of Atherosclerosis/Calcification

Variable	Beta	R^2 Change	p Value
Age	0.37	0.23	<0.0001
MAP	0.34	0.14	<0.0001
Heart rate	0.17	0.03	<0.0001
Glucose	0.10	0.01	<0.0001
CIMT	—	—	NS
Carotid/femoral plaque (y/n)	—	—	NS
Calcified plaque (y/n)	0.08	0.01	0.01

n = 900. Variables that did not enter the model include: smoking status, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, menopausal status, HRT, blood pressure treatment, and cholesterol treatment.

MAP = mean arterial pressure; other abbreviations as in Table 1.

original cohort tertile (7.5 ± 1.1 m/s vs. 7.4 ± 0.6 m/s), whereas that for the third tertile was slightly less than the original cohort tertile (10.1 ± 1 m/s vs. 10.8 ± 1.3 m/s). Aortic calcification (>1 mm^2 in 1 or more slices of the aorta) was present in 63% of subjects. Aortic calcium score was significantly greater in subjects with high cfPWV (within the third tertile in the main study) compared with age-matched subjects with low (first tertile) cfPWV ($p = 0.001$ for both Agatston and Volume score) (Table 3). On multivariate regression analysis across the whole group—adjusting for age, MAP, heart rate, glucose, and menopausal status—PWV was independently correlated with aortic calcification (beta = 0.49, $p < 0.001$, and beta = 0.42, $p < 0.01$, for Agatston and volume score, respectively). Results were similar when adjusted for twin–twin correlations.

Relationship of BMD to cfPWV, IMT, and carotid/femoral plaque. BMD was negatively correlated with age ($r = -0.31$ and $r = -0.24$ at the hip and lumbar spine, respectively $p < 0.0001$), but despite the correlation of cfPWV with age ($r = 0.49$, $p < 0.0001$), cfPWV did not correlate with BMD at the hip (or lumbar spine) either on univariate analysis or multivariable analysis (data not shown). There was also no significant independent correlation between BMD (at hip or lumbar spine) and carotid/femoral plaque (either noncalcified or calcified plaque). There was a weak but significant positive correlation between BMD and carotid IMT (beta = 0.09, $p < 0.05$, and beta = 0.13, $p < 0.01$, for hip and spine, respectively) that remained significant after adjustment for twin–twin correlations and when subjects taking antihypertensive treatment were excluded.

Heritability. The intraclass correlation coefficients for BMD (hip and spine), cfPWV, and CP were higher in MZ compared with DZ twin pairs ($r = 0.91$ and $r = 0.55$; $r = 0.87$ and $r = 0.57$; $r = 0.86$ and $r = 0.56$; and $r = 0.80$ and $r = 0.59$, respectively), suggesting a genetic influence on these traits. The fully adjusted ACE model confirmed an additive genetic component or heritability (h^2) accounting for 82% (95% CI: 0.69 to 0.85) and 77% (95% CI: 0.64 to 0.82) of the variance of BMD at the hip and spine, respectively, and 38% (95% CI: 0.19 to 0.59) of the variance in cfPWV. Heritability of all plaque was only 5% (95% CI: 0.00 to 0.61), but that of CP was 61% (95% CI: 0.04 to 0.83), although the CIs for this categorical measure were wider than those for the continuous measures. The within-twin correlation (r_{ph}) between cfPWV and CP was 0.39. Cross-twin, cross-trait correlations were higher in MZ ($r_{PWV/CP} = 0.37$) compared with DZ ($r_{PWV/CP} = 0.29$) twins, suggesting that an additive genetic influence contributes to the observed correlation between cfPWV and CP. The bivariate model that provided the best fit to the observed data was the AE model (Fig. 1), with 92% of the phenotypic correlation between cfPWV and CP explained by additive genetic effects.

Discussion

Arterial stiffness, as measured by cfPWV, is one of the most important predictors of future CVD events (1) but shows little or no relation to conventional risk factors other than age and blood pressure (18). Furthermore, animal models of atherosclerosis suggest that arterial stiffness is not affected by early atherosclerosis (19). Results of the present study confirm the close association of cfPWV with age and MAP and lack of or weak association with other risk factors such as smoking, lipid fractions, and fasting glucose consistent with previous studies (18). We also examined the relation of cfPWV to subclinical measures of atherosclerosis: carotid IMT and presence of atheromatous plaque in the carotid and femoral arteries. Carotid IMT is one of the earliest manifestations of subclinical atherosclerosis (20), although it might also be an adaptive response to increased blood pressure (21). The presence of plaque might be regarded as a more advanced manifestation of nonob-

Table 3 Subject Characteristics, Bone Chemistry, and Aortic Calcification in CT Substudy

Variable	Low cfPWV (n = 20)	High cfPWV (n = 20)
PWV (m/s)	7.5 ± 1.2	10.1 ± 1.0*
Age (yrs)	60 ± 6.7	61.5 ± 8.8
Height (cm)	163.6 ± 7.7	164.3 ± 4.9
Weight (kg)	66.6 ± 6.1	70.2 ± 12.0
MAP (mm Hg)	92.7 ± 8.8	94.8 ± 9.2
HR (beats/min)	61.2 ± 8.0	71.5 ± 16.0†
Fasting glucose (mmol/l)	5.13 ± 0.51	5.05 ± 0.64
Vitamin D (ng/ml)	19.2 ± 8.0	23.9 ± 10.0
Calcium (mmol/l)	2.4 ± 0.1	2.4 ± 0.1
Phosphate (mmol/l)	1.2 ± 0.1	1.2 ± 0.2
CTX (ng/ml)	0.44 ± 0.2	0.46 ± 0.2
Osteocalcin (ng/ml)	17.7 ± 6.8	15.4 ± 6.0
BAP (μg/l)	14.9 ± 6.2	13.4 ± 4.4
Agatston score (AU)	63.2 (483)	450.4 (3,518)‡
Volume score (cm^3)	0.05 (0.05)	0.38 (2.70)‡

Values are mean ± SD or median (interquartile range). Compared with low cfPWV, *$p < 0.0001$; †$p < 0.05$; ‡$p < 0.001$.

AU = arbitrary units; BAP = bone-specific alkaline phosphatase; CTX = C-terminal telopeptide of type 1 protein; HR = heart rate; other abbreviations as in Table 1.

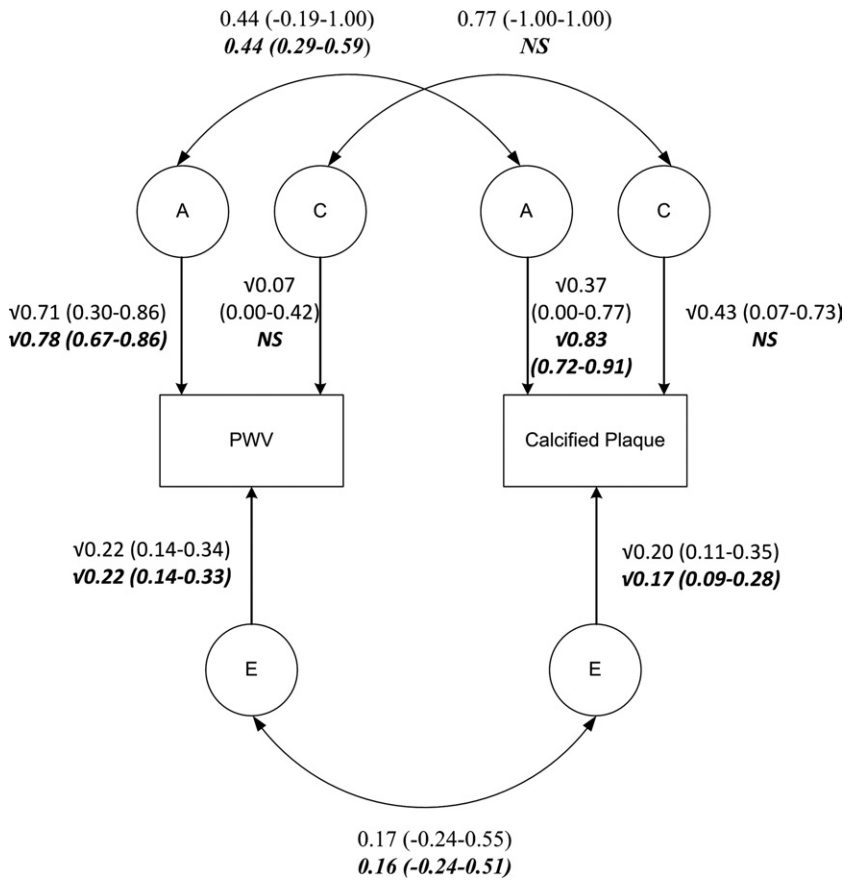

Figure 1 **Path Diagram of Bivariate Genetic Model for PWV and Calcified Plaque, Including Genetic and Environmental Correlations**

Results for the ACE model are displayed in *italic* and for the AE model in ***bold italics*** (with 95% confidence intervals). A = additive genetic; C = shared environment; E = nonshared environment. **Squares** = observed variables; **circles** = latent variable; **single-headed arrows** = causal paths; and **double-headed arrows** = correlations.

structive atherosclerosis. We found no independent association of cfPWV with IMT or with the presence of noncalcified atheroma. These observations suggest that atherosclerotic change within the arterial wall is not necessarily associated with arterial stiffening, in keeping with animal models of atherosclerosis (19) and previous human studies (22). Indeed, increased distensibility has been noted at the site of atherosclerotic plaques in the carotid artery (23).

An alternative explanation for arterial stiffening is that it is associated with calcification within atherosclerotic plaque (intimal calcification) and/or by medial calcification, which might be caused by a process distinct from atherosclerosis. However, the majority of previous studies have not attempted to distinguish whether the association of arterial stiffness with calcification is independent of atherosclerosis. A major finding of the present study is that—despite lack of correlation with risk factors for atherosclerosis, IMT, and presence of noncalcified plaque—we observed a significant association of cfPWV with CP detected by ultrasound in the carotid and femoral arteries and with total aortic calcification measured by CT. These findings are consistent with a previous study suggesting an association of arterial stiffness with echogenic plaque in the carotid artery (11).

The calcification detected in the present study by ultrasound was localized to atherosclerotic atheroma, whereas that detected by CT could have been intimal and/or medial (early medial calcification often being fragmented rather than diffuse [24]). Thus our study does not distinguish whether arterial calcification associated with arterial stiffening is primarily of the intimal or medial type. Lack of association of cfPWV with risk factors for atherosclerosis, with carotid IMT, and with carotid/femoral plaque suggests that, if plaque calcification influences arterial stiffness directly, it is the propensity of plaque to calcify rather than the amount of plaque that determines arterial stiffness. However, it is possible that degeneration of elastin (with an associated increase in arterial stiffening) renders it more susceptible to calcification (25). Calcification could thus be secondary to early degenerative change in elastin and act to amplify arterial stiffening initially caused by elastin degradation.

Vascular calcification is now recognized to be an active process regulated by molecular mechanisms that parallel those of bone mineralization (5). Vascular calcification can be induced by genetic manipulation of proteins regulating bone resorption, producing reciprocal effects on bone density and vascular calcification (26). It has been suggested that parallel processes of arterial calcification and bone demineralization explain the association between CVD and osteoporosis. Although several studies report an inverse association between vascular calcification and BMD (27–29), this finding is not universal (30–33), and vascular calcification has been observed in conditions of low bone turnover (34). Examining the relation between arterial stiffness and BMD might be a more sensitive way of testing the hypothesized reciprocal relationship between BMD and vascular calcification/arterial stiffening, because arterial stiffness could be influenced by minor degrees of calcification. Thus far, such studies have been of modest sample size, used different methodology to assess BMD and arterial stiffness, and have yielded conflicting results (35–39). As far as we are aware, this is the largest study to examine the relationship between aortic stiffness as measured by cfPWV and BMD determined with dual X-ray absorption. We found no significant association between cfPWV and BMD, either in univariate analysis or after accounting for possible confounders in multivariable analysis.

An alternative hypothesis linking osteoporosis to CVD events is that atherosclerosis within arteries supplying skeletal sites affects regional bone metabolism (5). Again, previous studies have yielded conflicting results (40,41). In the present study, BMD was not associated with presence of plaque and was weakly independently positively correlated to IMT, a correlation opposite to that expected if atherosclerosis were to cause osteoporosis. It is notable that a similar positive association was seen between BMD and IMT in younger women in the San Antonio Family Osteoporosis study (42). Therefore, results of the present study do not support a clear or direct relationship between osteoporosis and atherosclerosis or arterial stiffness.

Results of the heritability analysis in this study confirm the high heritability of BMD and moderate heritability of cfPWV. A novel finding is that the presence of CP was estimated to be of heritability similar to cfPWV. Although the confidence limits for the heritability estimate for CP were wide, they do suggest that arterial calcification has an important genetic component that might be distinct from that for atherosclerosis. Furthermore, this study shows that the phenotypic correlation between arterial stiffness and arterial calcification can be attributed to a common genetic influence. Lack of heritability of noncalcified plaque and lack of correlation of this with cfPWV suggest that CP probably develops de novo rather than as a progression of noncalcified plaque (in which case some intermediate association with cfPWV and genetic factors would be expected).

Study limitations. The study is limited to female twins. However, the Twins UK cohort is comparable to the general population of women in the U.K. for disease and lifestyle characteristics such as blood pressure, hypertensive drug use, and tobacco consumption (10). Findings in men might differ, and a recent study by Collins et al. (43) suggests peripheral arterial disease and increased peripheral arterial stiffness are associated with bone loss and fractures in the hip. We were not able to ascertain, due to limitations of current imaging modalities, the extent of medial calcification and its association with arterial stiffness. Finally, the cross-sectional nature of the study limits conclusions on causality; prospective and interventional studies will be required to define the role of arterial calcification in arterial stiffening.

Conclusions

In women, arterial stiffness is independent of noncalcified atheroma but relates to arterial calcification, and this association is due to a common genetic influence on calcification and stiffness. BMD is not independently related to arterial stiffness or to measures of atherosclerosis.

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