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Sex-Specific Associations Between Cardiac Workload, Peripheral Vascular Calcification, and Bone Mineral Density: The Gambian Bone and Muscle Aging Study

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Abstract

Noncommunicable diseases (NCD) are rapidly rising in Africa, with multimorbidity increasing the burden on health and social care. Osteoporosis and cardiovascular disease (CVD) share common risk factors; both often remain undiagnosed until a major life-threatening event occurs. We investigated the associations between cardiac workload, peripheral vascular calcification (PVC), and bone parameters in Gambian adults. The Gambian Bone and Muscle Aging Study (GamBAS) recruited 249 women and 239 men aged 40 to 75+ years. Body composition and areal bone mineral density (aBMD) were measured using dual-energy X-ray absorptiometry; peripheral quantitative computed tomography (pQCT) scans were performed at the radius and tibia. Supine blood pressure and heart rate were measured and used to calculate rate pressure product and pulse pressure. Presence of PVC was determined from tibia pQCT scans. Sex interactions were tested (denoted as *p*-int); adjustments were made for residuals of appendicular lean mass (ALM) and fat mass (FM). There were negative associations between rate pressure product and aBMD in women only, all *p*-int < .05; after adjustment for ALM residuals, for every 10% increase in rate pressure product, aBMD was lower at the whole body (−0.6% [−1.2, −0.1]), femoral neck (−0.9% [−1.8, −0.05]), L_1 to L_4 (−0.6% [−1.7, 0.5]), and radius (−1.9% [−2.8, −0.9]); there were similar associations when adjusted for FM residuals. Similar negative associations were found between pulse pressure and aBMD in women only. PVC were found in 26.6% men and 22.5% women; women but not men with calcification had poorer cardiac health and negative associations with aBMD (all sites *p*-int < .001). There were consistent associations with cardiac parameters and pQCT outcomes at the radius and tibia in women only. Multiple markers of cardiac health are associated with poorer bone health in Gambian women. In the context of epidemiological transition and changing NCD burden, there is a need to identify preventative strategies to slow/prevent the rising burden in CVD and osteoporosis in Sub-Saharan Africa. © 2020 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

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Introduction

Sub-Saharan African countries are currently experiencing one of the most rapid demographic transitions characterized by increasing urbanization and changing lifestyle factors. This has resulted in an increase in the incidence of noncommunicable diseases (NCD), especially cardiovascular disease (CVD), and a predicted rise in fragility fractures as the population ages.[1] Osteoporosis and CVD share common risk factors, including aging, smoking, sedentary behavior, and pathophysiological mechanisms (eg, sex hormones).[2] These chronic diseases remain undiagnosed until a major life-threatening event occurs; for example, heart failure owing to hypertension or fragility fracture as a result of osteoporosis. Chronic disease burden is a global

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issue, not just affecting older adults in high-income countries (HIC). Most studies to date have focused on older populations in HICs, whereas data from low-middle-income countries (LMIC) are sparse; the lack of data potentially contributes to inadequate guideline-based care and a wide treatment gap in LMICs.[3,4]

Populations of African ethnicity have a higher risk of developing hypertension compared with Whites.[5] A study in >6000 Gambians from the Kiang West region reported that blood pressure (BP) increased with age in both men and women aged >18 years, with a greater prevalence of elevated BP in women (18.9%) than in men (16.7%).[6] Secondary analysis of the 2010 WHO STEP Survey conducted among 3573 Gambian adults aged 25 to 64 years showed that the prevalence of hypertension was 29%; a higher proportion of hypertensive individuals were men and from rural compared with urban areas[7] and 79% of individuals with hypertension were previously undiagnosed. Importantly, a study 13 years earlier reported hypertension prevalence in Gambians aged 15 years and older to be 9.5%.[8] Together, these studies show a high and increasing prevalence of hypertension in The Gambia, particularly in men and in individuals living in rural areas.

Rate pressure product has been shown to be a strong correlate of myocardial oxygen consumption—the most important indicator of cardiac workload.[9] Increased BP and heart rate (HR) do not always occur simultaneously, signifying the value of rate pressure product.[10] Typically, increased HR during exercise indicates more blood and oxygen traveling to the working muscles, whereas increased BP occurs when more blood is pumped to the heart. Thus, a rise in HR triggers blood vessels to widen to help keep BP under control; healthy people can recover much faster from exercise compared with those with a medical condition. Pulse pressure is an indicator of arterial stiffness[11] and has been shown to be an independent marker of cardiovascular risk in individuals aged >50 years, particularly myocardial infarction[12] and coronary heart disease.[13] Between 30 and 50 years, systolic blood pressure (SBP) and diastolic blood pressure (DBP) track together in a nearly parallel manner; however, after 60 years of age, DBP decreases, while SBP continues to rise, accounting for the age-associated increase in pulse pressure due to higher aortic stiffness.[13]

Early evidence has suggested that high-resolution peripheral quantitative computed tomography (HR-pQCT)-detected peripheral vascular calcifications (PVC) are predictive of incident cardiovascular events.[14] Additionally, PVC from HR-pQCT images have been correlated with coronary artery calcifications identified using conventional multidetector computed tomography.[15] A study in UK Whites older adults reported that women with PVC determined by HR-pQCT had lower cortical area and lower trabecular number, consistent with greater trabecular spacing at the tibia, whereas there were no differences in men.[16] To date, all studies have been reported from HICs; there are no data from LMICs using peripheral quantitative computed tomography (pQCT)—a lower-cost imaging device in limited resource settings.

In Whites older adults from Australia, data show that hypertension was associated with reduced femoral neck areal bone mineral density (aBMD) and increased fracture risk in women.[17] A study in older Australians with a mean age of 70.5 years reported that aBMD at the femoral neck and total hip were inversely associated with rate pressure product in women but not in men.[18] There are no studies from Africa reporting on the association between cardiovascular risk factors and aBMD.

Therefore, given the rising incidence of NCD of aging in Sub-Saharan Africa, it is important to identify possible shared etiologies between NCDs such as cardiovascular and musculoskeletal disease. Therefore, the aims of this study were to describe sex differences in the associations between cardiac workload, arterial stiffness, PVC, and bone parameters in aging Gambian adults.

Materials and Methods

Participants and study design

Participants are from the Gambian Bone and Muscle Aging Study (GamBAS), a longitudinal prospective observational study investigating musculoskeletal aging in men and women from a rural region of The Gambia[19] (ISRCTN17900679). The Kiang West Demographic Surveillance System (KWDSS)[20] was initially used to identify men and women >40 years residing within the four core survey villages of this region. Individuals were ranked according to the accuracy of date of birth ascertained from the KWDSS, from most to least accurate (that is, exact day, month, or year), where recruitment priority was given to those with the most accurate. To reach target group sizes, individuals from six other villages in the area were also recruited from the region. After initial village sensitization and discussion with the elders, participants were located and approached by fieldworkers who explained the study in the local language and invited them to participate, with an approximate recruitment rate of 1 in 2 (~47% of those we have data on).[19] Frail, pregnant, or lactating individuals were excluded. The study received ethical approval by the joint Gambia Government/MRC The Gambia Ethics Committee (#SCC1222). Written informed consent was obtained from all participants. All outcomes were measured at a single research visit. Weight (kg) was measured using electronic scales and standing height (cm) was measured using a stadiometer.

Blood pressure

Participants' blood pressure was measured using the OMRON 705IT blood pressure monitor (OMRON Healthcare Europe B.V. Hoofddorp, Netherlands). Participants were in a supine position and rested for 5 minutes and then blood pressure measured in triplicate; the mean of the three measurements was used for analysis. Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (beats per minute [bpm]) were recorded. Rate pressure product was calculated as heart rate multiplied by SBP (bpm × mmHg).[10] Rate pressure product is an indication of cardiac workload, where a higher rate pressure product corresponds to a higher cardiac workload.[21] Pulse pressure was calculated as the difference between SBP and DBP.[12] Hypertension was defined as SBP ≥140 mmHg or a DBP ≥90 mmHg.[22]

Dual-energy X-ray absorptiometry (DXA)

Each participant had a whole-body scan by DXA as previously described[23] (GE Lunar Prodigy, Waltham, MA, USA; software version 10). Areal bone mineral density (g/cm^2) was assessed at the whole body, total hip, femoral neck, lumbar spine (L_1 to L_4), and radius. Body composition outcomes were total fat mass (FM, kg) and appendicular lean mass (ALM), which was calculated as arms plus legs lean mass (kg). Scans were excluded because of motion artifact, a participant having leprosy, and geophagy. Short-term precision measured as coefficient of variation (CV%) of duplicate

Table 1. Descriptive Characteristics

	Men (*n* = 239)	Women (*n* = 249)	*p* Value
General characteristics			
Age (years)	60.8 ± 12.3	61.1 ± 12.5	.798
Weight (kg)	59.9 ± 10.3	54.7 ± 10.3	<.0001
Height (cm)	169.2 ± 7.0	157.8 ± 6.0	<.0001
BMI (kg/m^2)	20.9 ± 3.1	21.9 ± 3.7	.0009
Current smoker or tobacco sniffer, *n* (%)	55 (23)	39 (16)	.147
Total fat mass (kg)	8.3 ± 6.0	17.1 ± 7.4	<.0001
ALM (kg)	22.9 ± 3.6	15.6 ± 2.4	<.0001
Cardiac parameters			
SBP (mmHg)	132.8 ± 23.1	135.1 ± 22.7	.268
DBP (mmHg)	72.2 ± 10.5	73.5 ± 10.3	.192
HR (bpm)	64.3 ± 12.4	68.7 ± 11.6	.0001
RPP (bpm × mmHg)	8500 ± 2094	9274 ± 2228	.0004
Pulse pressure (mmHg)	60.5 ± 17.4	61.6 ± 17.2	.496
MAP (mmHg)	92.4 ± 13.6	94.0 ± 13.3	.192
Hypertension prevalence, *n* (%)	71 (30)	91 (37)	.109
Calcified vessels, *n* (%)	59 (26.6)$^{n = 222}$	52 (22.5)$^{n = 231}$	.601
DXA bone parameters			
Whole-body aBMD (g/cm^2)	1.13 ± 0.10	0.99 ± 0.11	<.0001
Total hip aBMD (g/cm^2)	0.98 ± 0.14	0.82 ± 0.17	<.0001
Femoral neck aBMD (g/cm^2)	0.90 ± 0.14	0.81 ± 0.15	<.0001
L_1 to L_4 aBMD (g/cm^2)	1.01 ± 0.16	0.86 ± 0.18	<.0001
Radius aBMD (g/cm^2)	0.67 ± 0.09	0.50 ± 0.11	<.0001
pQCT bone parameters			
4% tibia trabecular vBMD (mg/cm^3)	176.0 ± 34.3$^{n = 215}$	151.7 ± 39.9$^{n = 228}$	<.0001
4% tibia total vBMD (mg/cm^3)	271.2 ± 45.5$^{n = 216}$	232.8 ± 49.2$^{n = 228}$	<.0001
38% tibia cortical vBMD (mg/cm^3)	1209.7 ± 36.0$^{n = 218}$	1171.4 ± 60.4$^{n = 228}$	<.0001
38% tibia CSA (mm^2)	453.3 ± 56.9$^{n = 218}$	359.5 ± 48.0$^{n = 228}$	<.0001
38% tibia cortical area (mm^2)	301.1 ± 39.6$^{n = 219}$	207.1 ± 37.4$^{n = 228}$	<.0001
4% radius trabecular vBMD (mg/cm^3)	166.0 ± 42.9$^{n = 197}$	114.8 ± 35.8$^{n = 212}$	<.0001
4% radius total vBMD (mg/cm^3)	313.0 ± 55.7$^{n = 197}$	251.6 ± 53.7$^{n = 212}$	<.0001
33% radius cortical vBMD (mg/cm^3)	1216.1 ± 37.1$^{n = 203}$	1182.1 ± 61.9$^{n = 210}$	<.0001
33% radius CSA (mm^2)	138.4 ± 18.5$^{n = 203}$	109.1 ± 14.1$^{n = 210}$	<.0001
33% radius cortical area (mm^2)	93.2 ± 12.8$^{n = 204}$	62.7 ± 12.3$^{n = 212}$	<.0001

BMI = body mass index; ALM = appendicular lean mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; RPP = rate pressure product; MAP = mean arterial pressure; aBMD = areal bone mineral density; vBMD = volumetric bone mineral density; CSA = cross-sectional area.

Values are mean ± standard deviation or frequency and percent (%). Bold indicates $p < .05$ tested by one-way ANOVA or chi-square test. Hypertension classified as SBP >140 mmHg or DBP >80 mmHg.

measurements in 70 Gambian adults was <1% for all sites for aBMD.

Peripheral quantitative computed tomography

Peripheral quantitative computed tomography (pQCT) measurements were made and scans analyzed, as previously described, at the tibia using a Stratec XCT-2000 scanner (Stratec, Pforzheim, Germany), software version 6.20c.[24] All measurements were taken in the non-dominant limb. Leg length was defined as the distance from the most proximal edge of the medial malleolus to the intercondylar eminence. Forearm length was defined as the distance from the distal edge of the ulna styloid process to the olecranon. Measurements were taken at 4%, 33%/38%, and 66% of the limb length (measured with a tape measure). The following outcomes were measured at the 4% radius and tibia: trabecular volumetric bone mineral density (Trab.vBMD, mg/cm^3), total vBMD (Total.vBMD, mg/cm^3); at the 33% radius and 38% tibia: cortical vBMD (Ct.vBMD; mg/cm^3), cross-sectional area (CSA; mm^2), and cortical area (Ct.Area; mm^2). For this analysis, we excluded scans that were affected by excessive motion that had distorted the image. The range of CVs of duplicate measurements of bone outcomes in 62 Gambian adults was 1% to 4% for the radius and 1% to 3% for tibia measurements.

As an indicator of peripheral artery disease, the presence of PVC was quantified by visualizing calcium plaque(s) as a bright spot in the pQCT images. Participants who had at least one visualized calcium plaque found in any of the scans taken from the tibia were considered to have calcified vessels, while those who had none served as having no calcified vessels. Scans were excluded where significant motion artifact was detected and distorted the image. We used a previously published criterion to determine the presence of PVC in tibia scans from HR-pQCT,[15] that is, linear or tubular hyper-dense zones of circular, semicircular, or crescent-like structures that corresponded to anatomical territories of the anterior tibial artery, posterior tibial artery, interosseous branches, or smaller intramuscular or subcutaneous arterioles.

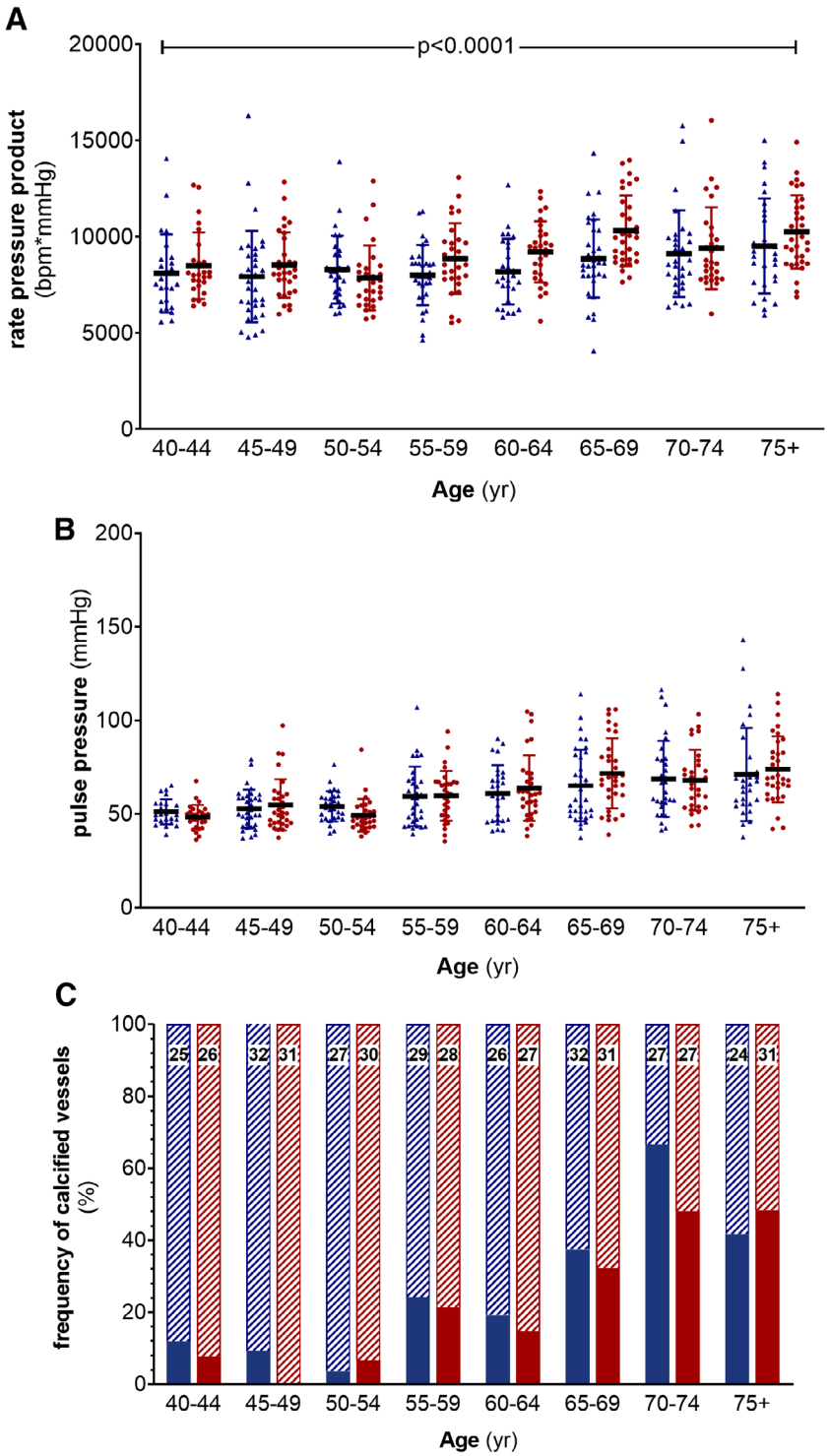

Fig 1. (*A*) Rate pressure product (RPP), (*B*) pulse pressure, and (*C*) presence of peripheral calcified vessels in Gambian men and women stratified by 5-year age band. Anova analysis showed a significant age*sex interaction ($p < .0001$) in RPP, whereas there were no sex differences with age in pulse pressure ($p = .496$) or in the presence of calcified vessels tested by chi-square ($p = .327$). Scatter dot plots in *A* and *B* are presented as mean ± SD and in *C* displayed as percent of individuals with peripheral vascular calcification (solid bars) versus those without (hatched bars) per age band (group numbers displayed per age band). Blue triangles and bars represent men; red circles and bars represent women.

Data analysis

All analyses were performed in Stata, version 15.0 (StataCorp, College Station, TX, USA); statistical significance was set at $p < .05$. Descriptive statistics were used to describe participant characteristics and are presented as mean ± standard deviation (SD), and categorical variables as frequency (*n*) and percent (%).

Table 2. Descriptive Characteristics of Men and Women, With and Without Peripheral Vascular Calcification (Calcified Vessels)

	Men			Women		
	No calcified vessels (n = 163)	Calcified vessels (n = 59)	p Value	No calcified vessels (n = 179)	Calcified vessels (n = 52)	p Value
General characteristics						
Age (years)	57.7 ± 11.5	68.1 ± 10.9	**<.0001**	58.1 ± 11.5	70.2 ± 10.8	**<.0001**
Weight (kg)	61.1 ± 10.8	57.8 ± 8.2	**.044**	55.8 ± 10.4	51.9 ± 10.2	**.012**
Height (cm)	170.2 ± 7.0	167.4 ± 6.8	**.009**	158.3 ± 6.0	156.3 ± 6.0	**.035**
BMI (kg/m^2)	21.0 ± 3.2	20.6 ± 2.7	.422	22.2 ± 3.7	21.2 ± 3.5	.065
Current smoker or tobacco sniffer, n (%)[a]	40 (25)	9 (16)	.084	24 (14)	9 (17)	.296
Total fat mass (kg)	8.2 ± 6.1	8.5 ± 5.7	.742	17.6 ± 7.5	15.6 ± 7.0	.083
ALM (kg)	23.5 ± 3.7	21.7 ± 2.7	**.0009**	15.9 ± 2.4	14.9 ± 2.3	**.010**
Cardiac parameters						
SBP (mmHg)	131 ± 23	132 ± 20	.922	132 ± 21	145 ± 24	**.0004**
DBP (mmHg)	72 ± 11	70 ± 9	.155	73 ± 11	73 ± 10	.790
HR (bpm)	64 ± 12	65 ± 14	.578	68 ± 12	70 ± 13	.222
RPP (bpm × mmHg)	8426 ± 2116	8578 ± 2095	.636	8853 ± 1786	10,065 ± 2250	**.0001**
Pulse pressure (mmHg)	59 ± 17	62 ± 16	.328	59 ± 15	72 ± 20	**<.0001**
MAP (mmHg)	92 ± 13	91 ± 11	.489	93 ± 13	97 ± 13	.063
Hypertension prevalence, n (%)	46 (21)	17 (28.8)	.931	56 (31.3)	28 (53.8)	**.003**

BMI = body mass index; ALM = appendicular lean mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; RPP = rate pressure product; MAP = mean arterial pressure.

Values are mean ± standard deviation. Bold indicates $p < .05$ tested by one-way ANOVA or chi-square test. Hypertension classified as SBP >140 mmHg or DBP >80 mmHg.

[a]Indicates n = 162 and n = 57 for men without and with calcified vessels, respectively, and n = 171 and n = 52 for women, without and with calcified vessels, respectively, for this variable.

Between-group differences in the participant characteristics were tested with a one-way ANOVA or chi-square test for categorical variables.

Regression analysis of ALM against height (m) and FM was carried out to produce standardized ALM residuals and repeated to produce FM residuals.[25] We used this residual method, as it removes the variance in ALM explained by FM and height, and vice versa for FM.[25] We then explored the relationship between rate pressure product, pulse pressure, or presence of PVC (independent variable) with bone parameters (dependent variable) using linear regression with adjustments for age and ALM or FM residuals. To test if these relationships were different between sex, we included a sex × (rate pressure product, pulse pressure, or presence of PVC) interaction term and reported the relevant p value (p-int). For these regression analyses described, bone variables and rate pressure product or pulse pressure were log transformed to normalize distributions and to allow expression of the results as percent difference per 10% change in rate pressure product or pulse pressure, with the results expressed as beta coefficients with 95% confidence intervals.[26] For the regressions with the sex × PVC interaction term, the mean differences between those without compared with those with PVC were expressed within sex using a post hoc command to test within-group differences (eg, men without PVC versus men with PVC; women without PVC versus women with PVC). To facilitate the visualization of the results, parameters were transformed into sex-specific Z-scores (per SD).

Results

In total, 488 participants were recruited, 239 men and 249 women. Descriptive characteristics are shown in Table 1. With increasing age, rate pressure product increased to a greater magnitude in women than in men (Fig. 1*A*), whereas there were no sex differences in pulse pressure or the presence of PVC (Fig. 1*B*, *C*, respectively). There were no sex differences in the proportion of participants with evidence of PVC (men 26.6% versus women 22.5%) (Table 1). A subanalysis of those with versus without PVC showed worse cardiac parameters in women, but there were no significant differences in men (Table 2).

In unadjusted analyses (Table 3), in women, every 10% increase in rate pressure product was negatively associated with aBMD at the whole body (−1.4%), femoral neck (−2.7%), and L_1 to L_4 (−1.8%), with the greatest difference at the radius (−3.5%) (all p-int < .05); significant differences remained after adjustment for age and ALM residuals (Table 3; Fig. 2), with similar differences after adjustment for age and FM residuals (Table 3; Supplemental Fig. S1). Comparable negative associations were found between pulse pressure and aBMD at all sites (Table 2).

Women with PVC had lower aBMD at all sites compared with those without calcified vessels; in contrast, there were no statistically significant differences in men. Notably, the greatest difference was observed in women with a −0.12% difference in radius aBMD compared with 0.05% in men (Table 3). There were similar differences whether adjustments were made for ALM or FM residuals.

Associations between cardiac parameters and pQCT outcomes at the tibia are shown in Table 4. In unadjusted analyses, in women, every 10% increase in rate pressure product was negatively associated with differences at the metaphysis (4% site): trabecular vBMD (−3.7% [−5.2, −2.2]) and total vBMD (−3.2% [−4.4, −2.0]); diaphysis (38%): cortical vBMD (0.5% [−0.8, −0.3]) and cortical area (−1.7% [−2.7, −0.7]). The magnitude of these differences was smaller once adjustments were made for age and ALM/FM residuals (Table 4). There were no sex differences

Table 3. Sex Differences in the Relationship Between DXA Bone Outcomes and Cardiac Parameters (Rate Pressure Product, Pulse Pressure and Calcified Vessels)

	aBMD (g/cm^2)	Unadjusted				Adjusted for age and ALM residuals				Adjusted for age and FM residuals			
		Men	Women	R^2	*p*-int	Men	Women	R^2	*p*-int	Men	Women	R^2	*p*-int
Rate pressure product	Whole body	0.1 (−0.4, 0.6)	−1.4 (−0.2, −0.8)	0.33	**<.0001**	0.7 (0.2, 1.2)	−0.6 (−1.2, −0.1)	0.50	**<.0001**	0.4 (−0.1, 0.8)	−0.7 (−1.2, −0.2)	0.51	**.003**
	Total hip	−0.6 (−1.5, 0.3)	−2.6 (−3.7, −1.5)	0.26	**.007**	0.7 (−0.1, 1.5)	−0.9 (−1.9, 0.05)	0.47	**.011**	0.4 (−0.5, 1.3)	−0.9 (−1.9, 0.08)	0.44	**.045**
	Femoral neck	−0.6 (−1.6, 0.3)	−2.7 (−3.8, −1.7)	0.16	**.003**	0.6 (0.1, 1.4)	−0.9 (−1.8, −0.05)	0.44	**.007**	0.3 (−0.5, 1.1)	−1.0 (−1.9, −0.06)	0.41	**.031**
	L_1 to L_4	0.3 (−0.7, 1.3)	−1.8 (−3.0, −0.7)	0.19	**.007**	1.2 (0.2, 2.1)	−0.6 (−1.7, 0.5)	0.32	**.015**	0.7 (−0.3, 1.6)	−0.7 (−1.8, 0.4)	0.34	.059
	Radius	−0.4 (−1.3, 0.6)	−3.5 (−4.6, −2.4)	0.48	**<.0001**	1.0 (0.2, 1.8)	−1.9 (−2.8, −0.9)	0.65	**<.0001**	0.5 (−0.3, 1.3)	−1.9 (−2.8, −1.0)	0.65	**<.001**
Pulse pressure	Whole body	−0.2 (−0.6, 0.3)	−1.4 (−1.8, −0.9)	0.34	**.001**	0.5 (0.03, 0.9)	−0.5 (−1.0,-0.07)	0.49	**.001**	0.5 (0.04, 0.9)	−0.4 (−0.9, −0.0005)	0.51	**.002**
	Total hip	−0.6 (−1.5, 0.2)	−2.4 (−3.2, −1.5)	0.27	**.005**	0.8 (−0.03, 1.5)	−0.6 (−1.4, 0.2)	0.47	**.010**	0.8 (0.02, 1.6)	−0.5 (−1.2, 0.3)	0.44	**.020**
	Femoral neck	−1.0 (−1.8, −0.1)	−2.6 (−3.4, −1.8)	0.18	**.008**	0.4 (−0.3, 1.2)	−0.7 (1.4, .05)	0.43	**.025**	0.5 (−0.2, 1.2)	−0.5 (−1.3, 0.2)	0.41	**.041**
	L_1 to L_4	−0.2 (−1.1, 0.7)	−2.2 (−3.1, −1.3)	0.21	**.003**	0.8 (−0.06, 1.7)	−0.8 (−1.7, 0.09)	0.32	**.008**	0.8 (−0.09, 1.7)	−0.8 (−1.6, 0.1)	0.35	**.010**
	Radius	−1.1 (−1.9, −0.2)	−2.9 (−3.8, −2.1)	0.48	**.002**	0.5 (−0.3, 1.3)	−1.1 (−1.8, −0.3)	0.64	**.003**	0.5 (−0.2, 1.3)	−1.0 (−1.7, 0.2)	0.64	**.004**
Presence of calcified vessels	Whole body	−0.02 (−0.05, 0.008)	−0.09 (−0.12, −0.06)	0.32	**.003**	0.02 (−0.005, 0.05)	−0.05 (−0.07, −0.02)	0.49	**.001**	0.01 (−0.01, 0.04)	−0.04 (−0.07, −0.01)	0.50	**.007**
	Total hip	−0.04 (−0.09, 0.01)	−0.17 (−0.22, −0.12)	0.29	**.001**	0.05 (0.001, 0.09)	−0.09 (−0.14, −0.04)	0.48	**<.0001**	0.03 (−0.01, 0.08)	−0.08 (−0.13, −0.03)	0.44	**.001**
	Femoral neck	−0.05 (−0.10, 0.005)	−0.17 (−0.22, −0.12)	0.18	**.001**	0.04 (−0.002, 0.08)	−0.07 (0.12, −0.03)	0.44	**<.0001**	0.03 (−0.01, 0.07)	−0.07 (−0.11, −0.02)	0.41	**.003**
	L_1 to L_4	−0.02 (−0.08, 0.03)	−0.15 (−0.2, −0.09)	0.21	**.003**	0.04 (−0.01, 0.10)	−0.08 (−0.14, −0.02)	0.33	**.001**	0.03 (−0.02, 0.08)	−0.07 (−0.12, −0.02)	0.35	**.005**
	Radius	−0.04 (−0.09, 0.01)	−0.21 (−0.26, −0.16)	0.50	**<.0001**	0.05 (0.003, 0.09)	−0.12 (−0.17, −0.08)	0.65	**<.0001**	0.04 (−0.008, 0.08)	−0.11 (−0.16, −0.07)	0.65	**<.0001**

Data are expressed as percent difference in bone outcome per 10% difference in rate pressure product or pulse pressure and percent differences within sex in those with versus without calcified vessels. Values are beta-coefficients with 95% confidence intervals. The *p*-int are from the sex*cardiac parameter interactions. Bold indicates $p < .05$.

in bone size (CSA, in all of the different adjustment models, *p*-int > .2). Similar differences were found between pulse pressure and PVC with tibia pQCT outcomes (Table 4). Consistent sex differences in these associations were found at the radius (Supplemental Table S1).

Discussion

In this study, we report sex differences in the associations between rate pressure product and pulse pressure, which are indicators of cardiac workload and arterial stiffness, respectively, and PVC, with aBMD and pQCT bone parameters in a rural population of Gambian men and women aged >40 years. Rate pressure product, pulse pressure, and PVC were negatively associated with aBMD at all sites in women, with no differences in men. Similar negative associations were found in cortical and trabecular bone parameters at the tibia and radius in women but not in men.

Our data show that the negative associations of rate pressure product on aBMD were found in women only, who also had higher rate pressure product and HR compared with men, and may indicate increased sympathetic activity.[27] In support of this, a study has shown sex differences with age in sympathetic activity, with higher levels in women than in men.[28] Studies in animals and humans have both reported deleterious effects of increased sympathetic activity on bone formation.[29–32] A study from the USA in 10 pre- and 13 postmenopausal White women measured microneurographic recordings of sympathetic nerve activity and reported increased sympathetic activity in the postmenopausal group.[30] In unadjusted analyses, the study showed inverse correlations between sympathetic activity and aBMD at the total body, femoral neck, femur, spine, and radius; after adjustments for age, these differences were all attenuated except at the radius.[30] A series of extensive studies from the same group established that the negative effects of sympathetic activity on bone turnover were modulated through β1-adrenergic receptors.[33] Finally, data from the Study of Osteoporotic Fractures in White women aged >65 years show that increased HR was a major risk factor for hip fracture in individuals residing in urban areas of the US.[34]Although it would be inappropriate to presume risk factors for NCDs of aging in HICs will encapsulate those in very different LMICs such as The Gambia, these data from the US show important links that should be explored in other populations. Together, these studies suggest that negative associations between rate pressure product and pulse pressure with aBMD in Gambian women may be due to increased sympathetic activity.

Gambian women with PVC had worse parameters of cardiac health and ALM compared with women with no calcified vessels, whereas in men, the only difference was lower ALM in those with PVC compared with those without. The presence of PVC has been shown to alter peripheral blood flow, muscle metabolism, and gait.[35] In women, the greater negative associations between trabecular vBMD and PVC compared with cortical vBMD may be due to decreased blood flow in the trabecular compartment potentially caused by plaque buildup in the arteries. In support of this hypothesis, magnetic resonance imaging studies have shown that decreased bone perfusion at the lumbar vertebra is independently correlated with greater carotid atherosclerosis, lower vertebral aBMD, and greater bone marrow fat content.[36,37] The region of interest that trabecular vBMD is measured at the distal site of both the tibia

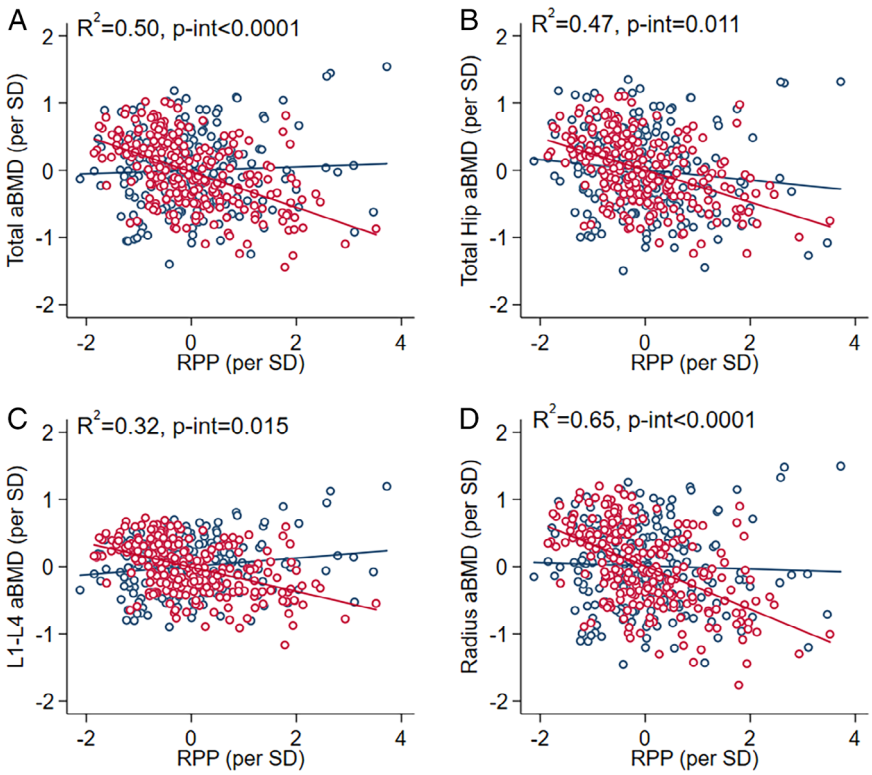

Fig 2. Relationship between rate pressure product (RPP) and aBMD at the (*A*) total body, (*B*) total hip, (*C*) L_1 to L_4, and (*D*) radius in Gambian men and women. Scatter plots included a sex*RPP interaction and were adjusted for age and ALM residuals and expressed as differences per SD. Blue represents men; red represents women.

and the radius with pQCT contains both bone mineral and marrow fat. Hence, for two bones with similar trabecular tissue vBMD but different marrow composition, a lower trabecular vBMD will result when assessed by pQCT. Therefore, although our data are indicating a greater effect in the trabecular compartment, this may be reflecting increased marrow adiposity. Future studies utilizing bone imaging techniques that have greater resolution and therefore capable of clear differentiation of bone and marrow, such as HRpQCT, are warranted.

The strengths of this study are the suite of measurements that are unique to Sub-Saharan Africa and allow detailed characterization of musculoskeletal health and the stratified study design ensured equal distribution of sampling across the age bands of men and women. There are potential limitations in this study. The observational design does not allow us to draw conclusions about causality or within individual change; the cohorts are being followed up. The primary outcome of GamBAS was to determine the changes in bone mineral density in men and women; the current study is a cross-sectional analysis of secondary outcomes. Kiang West is one region of The Gambia and the data may not be generalizable to urban areas of the country, to other West African countries, or to the remainder of the continent. Medication use is limited in the Kiang West region because of a lack of affordability and accessibility across The Gambia. Treatment for CVD is rarely in the form of beta blockers and estimated to be less than 5%, while the most commonly prescribed are calcium channel blockers, thiazide diuretics, and angiotensin-converting enzyme inhibitors. Despite low use, treatment of CVD by these medications may have confounded our findings. We did not collect data on physical activity and so we do not know whether this may have been a factor in the sex differences reported. Lean mass measured by DXA includes soft tissue as well as skeletal muscle, and body thickness and abnormalities in hydration status can affect measurement.[38] To partially overcome this limitation, we used appendicular lean mass (muscle mass in the limbs), which represents about 75% of the total body skeletal muscle mass.[39]

In conclusion, there are sex differences in the associations between cardiac workload and bone health in a rural population of Gambian men and women aged >40 years. In women, rate pressure product, pulse pressure, and presence of PVC were negatively associated with aBMD, cortical, and trabecular bone outcomes. Multiple markers of cardiac health are associated with poorer bone health in rural Gambian women. In the context of epidemiological transition and changing NCD burden, there is a need to identify preventative strategies to slow/prevent rising burden in CVD and osteoporosis.

Disclosures

All authors state that they have no conflicts of interest.

Table 4. Sex Differences in the Relationship Between Tibia pQCT Bone Outcomes and Cardiac Parameters (Rate Pressure Product, Pulse Pressure, and Calcified Vessels)

	pQCT bone outcome	Unadjusted				Adjusted for age and ALM residuals				Adjusted for age and FM residuals			
		Men	Women	R^2	*p*-int	Men	Women	R^2	*p*-int	Men	Women	R^2	*p*-int
Rate pressure product	4% tibia Trab.vBMD (mg/cm^3)	−0.7 (−2.0, 0.6)	−3.7 (−5.2, −2.2)	0.16	**.003**	0.5 (−0.7, 1.7)	−1.7 (−3.0, −0.3)	0.33	**.016**	−0.2 (−1.4, 1.0)	−1.8 (−3.2, −0.5)	0.35	.068
	4% tibia Total.vBMD (mg/cm^3)	−0.6 (−1.7, 0.4)	−3.2 (−4.4, −2.0)	0.20	**.002**	0.5 (−0.3, 1.4)	−1.2 (−2.2, −0.2)	0.45	**.010**	0.04 (−0.9, 0.9)	−1.3 (−2.3, −0.3)	0.46	**.047**
	38% tibia Ct.vBMD (mg/cm^3)	0.1 (−0.2, 0.3)	−0.5 (−0.8, −0.3)	0.17	**.001**	0.2 (0.02, 0.4)	−0.3 (−0.5, −0.002)	0.29	**.003**	0.2 (−0.03, 0.4)	−0.3 (−0.5, −0.01)	0.29	**.006**
	38% tibia CSA (mm^2)	−0.003 (−0.7, 0.7)	0.4 (−0.4, 1.2)	0.46	.460	0.3 (−0.4, 1.0)	0.8 (−0.04, 1.6)	0.51	.346	0.1 (−0.6, 0.9)	0.8 (−0.1, 1.6)	0.47	.253
	38% tibia Ct.Area (mm^2)	0.1 (−0.8, 0.9)	−1.7 (−2.7, −0.7)	0.60	**.010**	0.8 (−0.01, 1.6)	−0.5 (−1.4, 0.5)	0.67	**.039**	0.4 (−0.4, 1.3)	−0.5 (−1.5, 0.4)	0.65	.130
Pulse pressure	4% tibia Trab.vBMD (mg/cm^3)	−1.3 (−2.5, −0.05)	−3.4 (−4.6, −2.3)	0.18	**.011**	0.2 (−1.0, 1.3)	−1.5 (−2.6, −0.3)	0.32	**.040**	0.2 (−0.9, 1.4)	−1.4 (−2.5, −0.3)	0.35	**.036**
	4% tibia Total.vBMD (mg/cm^3)	−1.2 (−2.2, −0.2)	−3.3 (−4.2, −2.3)	0.24	**.002**	0.2 (−0.6, 1.1)	−1.3 (−2.2, −0.5)	0.45	**.008**	0.3 (−0.5, 1.2)	−1.2 (−2.1, −0.4)	0.46	**.006**
	38% tibia Ct.vBMD (mg/cm^3)	−0.03 (−0.2, 0.2)	−0.6 (−0.8, −0.4)	0.19	**<.0001**	0.2 (0.01, 0.4)	−0.3 (−0.5, −0.05)	0.29	**.001**	0.2 (0.0004, 0.4)	−0.3 (−0.5, −0.1)	0.29	**.001**
	38% tibia CSA (mm^2)	−0.1 (−0.8, 0.6)	0.1 (−0.5, 0.7)	0.46	.658	0.005 (−0.7, 0.7)	0.5 (−0.2, 1.1)	0.50	.307	0.1 (−0.6, 0.8)	0.6 (−0.1, 1.3)	0.47	.336
	38% tibia Ct.Area (mm^2)	−0.2 (−1.0, 0.6)	−1.9 (−2.7, −1.1)	0.61	**.004**	0.5 (−0.3, 1.3)	−0.7 (−1.5, 0.1)	0.67	**.034**	0.6 (−0.2, 1.4)	−0.5 (−1.3, 0.3)	0.65	**.038**
Presence of calcified vessels	4% tibia Trab.vBMD (mg/cm^3)	−0.03 (−0.10, 0.04)	−0.26 (−0.33, −0.19)	0.20	**<.0001**	0.07 (0.004, 0.13)	−0.15 (−0.22, −0.09)	0.35	**<.0001**	0.05 (−0.01, 0.12)	−0.14 (−0.21, −0.08)	0.37	**<.0001**
	4% tibia Total.vBMD (mg/cm^3)	−0.05 (−0.11, 0.003)	−0.23 (−0.29, −0.17)	0.26	**<.0001**	0.05 (−0.001, 0.09)	−0.12 (−0.18, −0.07)	0.47	**<.0001**	0.03 (−0.01, 0.08)	−0.12 (−0.17, −0.07)	0.48	**<.0001**
	38% tibia Ct.vBMD (mg/cm^3)	−0.006 (−0.02, 0.006)	−0.03 (−0.04, −0.01)	0.16	**.024**	0.008 (−0.004, 0.02)	−0.009 (−0.02, 0.004)	0.28	.057	0.008 (−0.004, 0.02)	−0.008 (−0.02, 0.005)	0.28	.065
	38% tibia CSA (mm^2)	−0.01 (−0.05, 0.02)	−0.03 (−0.07, 0.009)	0.46	.562	0.002 (−0.04, 0.04)	−0.03 (−0.07, 0.02)	0.50	.333	−0.007 (−0.05, 0.03)	−0.02 (−0.06, 0.02)	0.46	.682
	38% tibia Ct.Area (mm^2)	−0.02 (−0.07, 0.03)	−0.11 (−0.17, −0.06)	0.61	**.009**	0.04 (−0.008, 0.08)	−0.05 (−0.1, −0.001)	0.67	**.008**	0.02 (−0.02, 0.07)	−0.04 (−0.09, 0.009)	0.65	.053

Trab = trabecular; vBMD = volumetric bone mineral density; Ct = cortical; CSA = cross-sectional area.
Data are expressed as percent difference in bone outcome per 10% difference in rate pressure product or pulse pressure and percent differences within sex in those with versus without calcified vessels. Values are beta-coefficients with 95% confidence intervals. The *p*-int are from the sex*cardiac parameter interactions. Bold indicates $p < .05$.

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