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ORIGINAL ARTICLE

Quantitative ultrasound in relation to risk factors for low bone mineral density in South African pre-menopausal women

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Abstract
Summary The study describes the association between risk factors and quantitative ultrasound bone measures in black and mixed-race pre-menopausal South African women. Despite some differences between the two study groups, the findings generally lend support to the use of ultrasound for epidemiological studies of bone mass in resource-limited settings.
Introduction Quantitative ultrasound at the calcaneus is a convenient and inexpensive method of estimating bone strength well suited to community-based research in countries with limited resources. This study determines, in a large sample of pre-menopausal South African women, whether characteristics associated with quantitative ultrasound measures are similar to those shown to be associated with bone mineral density as measured by dual X-ray absorptiometry.
Methods This cross-sectional study included 3,493 women (1,598 black and 1,895 mixed race), aged 18–44 living in Cape Town. Study nurses administered structured interviews on reproductive history, lifestyle factors, and measured height and weight. Calcaneus quantitative ultrasound measurements were obtained using the Sahara device. Adjusted means of ultrasound measures according to categories of risk factors were obtained using multivariable regression analysis.
Results Associations between quantitative ultrasound measures and age, body mass index, age at menarche, parity, and primary school physical activity were similar to those known for bone mineral density as measured by dual X-ray absorptiometry. There were no clear associations between quantitative ultrasound measures and educational level, alcohol use, cigarette smoking, and current calcium intake.
Conclusion The data give qualified support to the use of quantitative ultrasound as an epidemiological tool in large studies of bone strength in pre-menopausal women.

Keywords Pre-menopausal · Quantitative ultrasound · Risk factors · South Africa · Women

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Introduction

Osteoporosis, a skeletal disorder commonly resulting in fractures of the spine, hip, or wrist, affects approximately one in four post-menopausal Caucasian women [1]. Currently, the World Health Organization diagnosis of osteoporosis rests on the evaluation of bone mineral density

(BMD) at the hip and the lumbar spine—sites that are clinically important in terms of fracture risk. Dual X-ray absorptiometry (DXA) is considered the "gold standard" for measuring BMD [2]. In South Africa, DXA machines are located in urban centers such as research facilities and hospitals. Factors influencing BMD, as measured by DXA, include age, body mass index, genetic factors, ethnicity, exposure to estrogen, and weight-bearing physical activity [3]. In addition, impaired absorption or low dietary intake of vitamin D and calcium and excessive use of alcohol and tobacco are risk factors for low BMD, although the association between moderate intake of these substances and BMD is unclear [4]. Most of the findings have come from studies of post-menopausal women, and the evidence regarding the relative importance of these factors in pre-menopausal women is less conclusive [5].

Quantitative ultrasound (QUS) has also been used to measure bone characteristics. QUS is significantly cheaper than DXA and non-invasive and the machine is readily portable, making it a practical tool for large epidemiological investigations, particularly in areas located far from facilities with DXA machines. QUS standard equipment measures bone characteristics at the calcaneus and not at the lumbar spine or hip, the two anatomical sites most commonly involved in debilitating osteoporotic fracture. Although the correlation between heel QUS measures and heel BMD as measured by DXA is high (0.79–0.86) [6], a number of studies have shown QUS measurements of the calcaneus to be only moderately correlated with DXA-derived BMD at the hip and lumbar spine [7–11]. However, QUS is thought to measure bone characteristics in addition to BMD such as the number, thickness and orientation of trabeculae, and the elasticity as well as the strength of bone [12–14].

A number of large prospective and retrospective studies have confirmed that the predictive power of calcaneal ultrasound measurement for osteoporotic fracture at the hip and lumbar spine is as good as that of DXA-derived BMD at these sites [15–17]. Other studies caution that the accuracy of prediction of fracture from calcaneal QUS is not very high, and that QUS should not be used in screening for individuals at risk of osteoporosis [18–20]. Currently, there is limited and controversial epidemiologic data on BMD and fracture incidence in the different ethnic populations in South Africa [21–26].

In resource-limited settings like South Africa, it is highly desirable to use the more portable and cheaper ultrasound method for conducting epidemiological studies of bone characteristics in clinically well women. The present study assessed whether risk factors associated with QUS measures of bone characteristics are similar to those known to be associated with BMD as measured by DXA, and compared these associations in black and mixed-race pre-menopausal women. Risk factors included age, demographic background, body mass index (BMI), reproductive and contraceptive history, physical exercise, smoking and alcohol intake, and calcium intake.

Methods

The data were derived from a study of women of reproductive ages recruited from health centers in the greater Cape Town area. The main purpose of the study was to assess whether depot contraceptive progestin use was associated with QUS measurements of the heel [27]. Information was collected on many potential correlates of QUS, in order that these risk factors could be controlled in the analyses of the relation of progestin use to QUS measures, and so that the relation of these potential correlates with QUS could be assessed. The present analysis assesses the correlation of those variables with QUS.

The study was conducted between September 2002 and September 2005 at community health facilities in Gugulethu and Mitchells Plain, both situated close to Cape Town in the Western Cape Province, South Africa. Each site was allocated a Sahara Ultrasound machine (Hologic, Bedford, MA, USA) to measure bone mass.

A structured questionnaire was administered by trained nurse interviewers in the subject's preferred language (English, Afrikaans, or Xhosa), and each subject's height, weight, and calcaneal ultrasound measurements were taken. The study protocol was approved by the institutional review boards of Boston University and the University of Cape Town.

Study subjects

The study nurses approached women in the centers to determine if they met eligibility requirements for the study and if they wanted to participate. The nurses recruited the women without knowledge of their contraceptive use histories.

Women eligible for the study were aged 18–44, pre-menopausal, had not been pregnant or had not breastfed in the previous year, and did not have an illness or use medication that would influence their bone health. Medical conditions for exclusion were illnesses requiring bed rest for more than 6 weeks in the past 12 months, thyroid, parathyroid, and pituitary disease, cancer, sarcoidosis, rheumatoid arthritis, chronic liver and kidney disease, rickets, Paget's disease, and osteoporosis. Women taking anticonvulsants, systemic corticosteroids, drugs for hypo-, hyper-, or parathyroidism, thiazide diuretics, or calcium supplements for more than 6 months in the last 5 years were also excluded. Written informed consent was obtained from all subjects.

Of the 4,362 women approached, 3,957 were willing to participate in the study. Four hundred and thirteen were

additionally excluded for failing to meet study criteria or because the Sahara measurement failed, leaving 3,544 women. We excluded 51 from the analysis because of ultrasound measures below or above the 0.5 percentile of measures (broadband ultrasonic attenuation [BUA] ≤45 and ≥117 dB/MHz or speed of sound (SOS) ≤1,500 and ≥1,645.5 m/s), leaving 3,493 women; 1,598 were black and 1,895 were of mixed racial ancestry, which could be a combination of any of the following: black, white, Asian, or Khoisan ancestry.

Interview

The study nurses administered standard questionnaires to collect information on demographic, reproductive, and contraceptive history, and smoking and alcohol intake. We categorized alcohol intake and smoking in terms of current, past, or never use. For both smokers and drinkers, current and past users were asked information on duration, frequency, and quantity of intake. Past drinkers and smokers were also asked number of years since last use. Current intake of selected calcium-rich foods was obtained using a questionnaire that has been validated against 3-day records (Micklesfield, unpublished data). Information on the frequency and quantity of milk, yogurt, cheese, and fish (such as pilchards which are rich in calcium) intake was obtained and the total number of weekly servings for these items was calculated. The physical activity section of the questionnaire was adapted from Kriska et al. [28] and has previously been applied within the South African context [29]. Historical information on physical activity was obtained for three epochs—primary school, high school, and post-school. The nurses recorded walking to school and other habitual walking activities lasting longer than 40 min, including walking for transport, for pleasure, and walking herding cattle, carrying wood, or fetching water. They also recorded participation in sports and leisure activities such as athletics, tennis, netball, volleyball, and dancing. In addition, for participants who had worked in jobs for 2 years or more, information was collected on walking and carrying heavy objects at work.

To take account of load bearing during activities, the impact of loading from each physical activity was ranked on a 0–3 scale with "0" indicating non-weight-bearing (e.g., swimming) and "3" indicating high impact such as playing volleyball [30]. Total impact hours (TIH) were calculated for each of the three epochs.

Measurement

Weight and height measurements were taken using a SECA (Hamburg, Germany) standard floor scale and SECA height measure with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight divided by height squared in kilograms per square meter.

Bone mass was assessed using a heel gel-coupled (dry) quantitative ultrasound system, the Sahara (Hologic, SN 03281, SN 03278). The Sahara ultrasound device measures two parameters: speed of sound (SOS) in meters per second and broadband ultrasonic attenuation (BUA) in decibels per megahertz. SOS is the distance between the two transducers divided by the time it takes for the signal to pass from one transducer through the heel to the opposite transducer. BUA is the slope of the regression line for the relationship between the ultrasound attenuation and the sound frequency over the range 0.1–1 MHz [31]. Higher values of BUA and SOS are associated with greater bone mass. The quantitative ultrasound index (QUI) is a linear combination of both BUA and SOS $(\mathrm{QUI} = (\mathrm{BUA} + \mathrm{SOS}) \times 0.41 - 571)$. BUA is correlated with heel BMD as measured by DXA (r values ~0.8) [32].

Quality control

The study nurses were trained in using the QUS machines until they achieved proficiency such that the coefficient of variation (CV) for repeated measures of the same subject was within the machine specification as specified by Hologic. For the Mitchells Plain machine, the CV for 40 repeated measures was 2.7% for BUA and 0.3% for SOS. For the Gugulethu machine, the CV was 2.1% for BUA and 0.3% for SOS for 21 repeated measures. On a daily basis, a phantom was used to check the quality control of each machine. The phantom values were required to fall within the quality control (QC) limits of 0.86–1.14 for QAB and 0.986–1.014 for QAS. QAB and QAS are dimensionless quantities calculated by dividing the phantom BUA and SOS measured in the daily quality control procedure by the values specified for that phantom by the manufacturer. If the machine did not pass the QC, it was recalibrated. If it continued to fail QC, the transducer pads were replaced. In addition, if, over a number of weeks, the mean QC values for a machine drifted outside Sahara specification, the machine was also recalibrated. Both machines were recalibrated twice over the study period.

To assess correlation of the QUS measures with DXA measures, a sample of 14 women was measured on both the Gugulethu and the Mitchells Plain QUS machines and in addition had a DXA scan (DXA Hologic, Model Discovery W S/N 80196) performed at the same visit. For the Gugulethu sonometer, the correlation coefficients between BMD assessed by DXA at the femoral neck, femoral trochanter, total hip (the combination of femoral neck, femoral trochanter, and intertrochanteric areas), and total lumbar spine (L1–4) and BUA of the calcaneus were 0.69, 0.78, 0.74, and 0.60; the corresponding correlation coef-

Table 1 Associations of risk factors with BUA, SOS, and QUI among 1,598 black women

Risk factor	*N* (%)	BUA mean (SD)	BUA adj LSM[a]	*p* for trend (adj LSM)	SOS mean (SD)	SOS adj LSM[a]	*p* for trend (adj LSM)	QUI mean (SD)	QUI adj LSM[a]	*p* for trend (adj LSM)
Age (years)				0.05			0.039			0.027
18–19	141 (8.8)	77.1 (12.3)	78.8		1,564 (25.1)	1,561		102.0 (14.2)	101.5	
20–24	422 (26.4)	80.5 (13.3)	81.4		1,563 (24.8)	1,563		103.1 (14.3)	103.1	
25–29	373 (23.3)	81.4 (12.6)	81.2		1,561 (25.2)	1,562		102.5 (14.2)	102.7	
30–34	299 (18.7)	80.6 (13.4)	80.1		1,561 (27.2)	1,562		102.1 (15.6)	102.3	
35–39	227 (14.2)	83.4 (14.1)	82.6		1,566 (25.4)	1,567		105.3 (15.1)	105.2	
40–44	136 (8.5)	85.2 (14.3)	83.8		1,568 (28.1)	1,568		106.9 (16.4)	106.3	
BMI (kg/m^2)				<0.001			0.044			<0.001
<23	235 (14.7)	76.2 (12.6)	76.4		1,562 (25.3)	1,562		100.5 (14.6)	100.6	
23–24	221 (13.8)	77.6 (13.0)	77.9		1,561 (25.6)	1,561		100.7 (14.7)	100.9	
25–29	533 (33.4)	80.7 (12.9)	80.8		1,563 (25.7)	1,563		102.9 (14.6)	103.1	
30–34	386 (24.2)	84.7 (13.2)	84.5		1,565 (25.0)	1,565		105.3 (14.5)	105.3	
35+	223 (13.9)	85.5 (13.1)	85.1		1,566 (28.1)	1,565		106.2 (15.6)	105.6	
Height (cm)				0.204			<0.001			0.037
<153	211 (13.2)	79.7 (13.9)	79.5		1,566 (26.5)	1,566		103.9 (15.1)	103.8	
153–157	386 (24.2)	82.3 (14.0)	81.9		1,567 (26.9)	1,567		105.2 (15.7)	105.0	
158–161	466 (29.1)	81.1 (12.8)	81.0		1,562 (24.9)	1,563		102.8 (14.3)	102.8	
162+	535 (33.5)	81.2 (13.1)	81.6		1,561 (25.2)	1,561		102.1 (14.6)	102.4	
Education				0.497			0.831			0.962
Grade 9 or less	453 (28.4)	81.5 (13.9)	80.8		1,565 (26.6)	1,564		103.9 (15.4)	103.2	
Grade 10–11	681 (42.6)	81.1 (13.3)	81.3		1,563 (25.6)	1,563		103.1 (14.8)	103.3	
Grade 12	464 (29.0)	81.2 (13.0)	81.5		1,563 (25.4)	1,563		103.0 (14.5)	103.3	
Age at menarche (years)				0.060			0.009			0.010
<13	120 (7.5)	82.8 (13.9)	83.4		1,567 (23.5)	1,566		105.4 (14.3)	105.5	
13–14	576 (36.1)	81.2 (12.9)	81.3		1,564 (25.7)	1,564		103.5 (14.7)	103.6	
15	340 (21.3)	80.9 (13.3)	80.8		1,564 (26.7)	1,564		103.3 (15.0)	103.3	
16+	427 (26.7)	80.8 (13.5)	80.6		1,560 (25.5)	1,560		101.9 (14.9)	101.7	
Live births				0.926			0.003			0.000
None	534 (33.4)	79.8 (13.0)	81.2		1,565 (24.5)	1,567		103.5 (14.2)	104.8	
1+	1,064 (66.6)	82.0 (13.5)	81.3		1,562 (26.4)	1,562		103.2 (15.2)	102.5	
Primary school PA (TIH[b])				0.183			0.842			0.534
1 (0–310)	236 (14.8)	79.8 (13.5)	79.8		1,562 (25.9)	1,562		102.1 (14.8)	102.0	
2 (311–1,118)	272 (17.0)	81.4 (13.1)	81.6		1,565 (26.7)	1,565		104.1 (15.0)	104.3	
3 (1,119–2,582)	389 (24.3)	80.9 (12.9)	81.0		1,563 (25.1)	1,563		103.0 (14.5)	103.0	
4 (2,583–31,579)	700 (43.8)	81.9 (13.7)	81.8		1,563 (25.9)	1,563		103.5 (15.0)	103.5	

Smoking status				0.818*			0.865*		0.847*
Non-smoker	1,439 (90.1)	81.3 (13.2)	81.2		1,563 (25.7)	1,563		103.2 (14.8)	103.2
Ex-smoker	59 (3.7)	80.8 (15.7)	81.6		1,566 (27.0)	1,565		104.0 (15.6)	103.9
Current smoker	100 (6.3)	81.3 (14.7)	82.1		1,565 (26.6)	1,564		103.8 (15.9)	104.0
Alcohol use				0.323*			0.304*		0.419*
Non-drinker	1,167 (73.0)	81.5 (13.2)	81.6		1,563 (26.0)	1,564		103.4 (14.8)	103.5
Ex-drinker	112 (7.0)	80.3 (14..5)	80.3		1,566 (25.4)	1,566		104.1 (15.3)	104.0
Current drinker	319 (20.0)	80.5 (13.7)	80.3		1,563 (25.4)	1,562		102.8 (15.0)	102.3
Quartile of calcium intake (weekly servings)				0.851			0.686		0.695
1 (0–5.25)	540 (33.8)	81.3 (13.9)	81.2		1,563 (25.9)	1,563		103.1 (15.1)	103.1
2 (5.3–10.75)	482 (30.1)	81.0 (12.8)	81.2		1,563 (26.1)	1,563		103.1 (14.7)	103.1
3 (10.8–15.25)	287 (18.0)	81.2 (13.7)	81.1		1,565 (26.0)	1,565		104.1 (15.0)	104.0
4 (15.3–50.25)	289 (18.1)	81.6 (13.2)	81.4		1,563 (25.1)	1,563		103.1 (14.6)	103.2

*p value for difference between groups using multivariate analysis of variance

[a] Control for age, BMI, height, education, age at menarche, number of live births, alcohol use, cigarette smoking, physical activity level at primary school, and calcium intake

[b] Total impact hours

ficients between BMD and SOS were 0.65, 0.84, 0.73, and 0.54. For QUI, these coefficients were 0.68, 0.84, 0.75, and 0.58 (all significant; $p<0.05$). Similarly, for the Mitchell's Plain sonometer, the correlation coefficients of the four DXA measurements with BUA were: 0.72, 0.77, 0.74, and 0.53; with SOS they were 0.62, 0.82, 0.70, and 0.50; and with QUI they were 0.67, 0.83, 0.74, and 0.52 (all $p<0.075$).

Statistical analysis

We calculated the crude mean value of BUA, SOS, and QUI for each category of a specific risk factor and obtained adjusted mean of BUA, SOS, and QUI using linear regression models. Variables included in the multivariable regression model were age, height, BMI, education, age at menarche, number of live births, smoking and alcohol use, calcium intake, and early physical activity. Adding contraceptive use to the model did not affect the results. We tested the linear dose–response relationship by entering the median value for the exposure category of interest into a term in the regression model. To further investigate residual confounding by BMI of height, physical activity, and age at menarche, the multivariable regression model was again tested according to three strata of BMI. All analyses were performed using STATA software version 9.0 (StataCorp LP, TX, USA)

Results

The characteristics of study sample by ethnicity are shown in Tables 1 and 2. Black women were younger, taller, had higher BMIs, and had completed more years of education than women of mixed race. In addition, black women experienced menarche later, had fewer live births, drank less alcohol and smoked less frequently, had a lower calcium intake, and engaged in more physical activity in primary school.

For black women (Table 1), the adjusted means for all QUS measures—BUA, SOS, and QUI—increased significantly with increasing age and with increasing BMI. All three measures decreased with increasing age at menarche. SOS and QUI decreased with increase in height and were also lower among parous women when compared with nulliparous women. BUA was not affected by these variables. There were small but non-significant positive associations of BUA, SOS, and QUI with physical activity in primary school. There was no association between the three QUS measures and education level, alcohol use, cigarette smoking, and current calcium intake.

For women of mixed race (Table 2), adjusted mean BUA and QUI increased with increasing age but for SOS the trend was not significant. BUA increased significantly with

Table 2 Association between risk factors and BUA, SOS, and QUI among 1,895 women of mixed race

Risk factor	*N* (%)	BUA mean (SD)	BUA adj LSM[a]	*p* for trend (adj LSM)	SOS mean (SD)	SOS adj LSM[a]	*p* for trend (adj LSM)	QUI mean (SD)	QUI adj LSM[a]	*p* for trend (adj LSM)
Age (years)				0.001			0.131			0.024
18–19	177 (9.3)	75.6 (13.6)	74.8		1,565 (26.9)	1,559		101.4 (15.5)	98.8	
20–24	512 (27.0)	75.9 (13.1)	75.7		1,560 (28.0)	1,558		99.9 (16.0)	99.0	
25–29	363 (19.2)	77.9 (13..3)	77.8		1,561 (26.1)	1,561		100.9 (15.1)	100.8	
30–34	311 (16.4)	78.1 (13.7)	78.1		1,560 (27.1)	1,562		100.8 (15.7)	101.5	
35–39	284 (15.0)	79.7 (14.8)	80.2		1,562 (28.9)	1,564		102.0 (17.1)	103.2	
40–44	248 (13.1)	78.6 (15.1)	79.2		1,558 (28.4)	1,561		99.9 (16.9)	101.5	
BMI (kg/m^2)				<0.001			0.467			0.164
<23	638 (33.7)	75.4 (13.7)	75.6		1,563 (28.3)	1,563		100.6 (16.3)	100.7	
23–24	263 (13.9)	75.8 (13.2)	75.8		1,559 (29.6)	1,559		99.2 (16.6)	99.1	
25–29	507 (26.7)	78.4 (13.9)	78.4		1,559 (26.4)	1,560		100.5 (15.6)	100.6	
30–34	306 (16.2)	80.2 (13.7)	79.8		1,560 (26.8)	1,560		101.5 (15.6)	101.2	
35+	181 (9.5)	80.9 (14.1)	80.8		1,561 (26.7)	1,561		102.3 (15.7)	102.3	
Height (cm)				0.260			<0.001			<0.001
<153	762 (40.2)	78.4 (14.2)	78.1		1,565 (27.7)	1,565		102.6 (16.1)	102.6	
153–157	491 (25.9)	77.3 (13.6)	77.3		1,560 (28.1)	1,560		100.2 (16.2)	100.3	
157.1–161.9	408 (21.5)	76.7 (13.3)	76.9		1,556 (25.3)	1,556		98.6 (14.8)	98.6	
162+	234 (12.4)	76.8 (14.2)	77.4		1,558 (28.6)	1,557		99.1 (16.8)	99.1	
Education				0.058			0.517			0.262
Grade 9 or less	1,000 (52.8)	77.2 (14.1)	77.0		1,560 (28.1)	1,560		100.1 (16.4)	100.3	
Grade 10–11	580 (30.6)	77.7 (13.2)	77.9		1,562 (26.2)	1,561		101.1 (15.1)	101.1	
Grade 12	315 (16.6)	78.4 (14.2)	78.6		1,563 (28.3)	1,561		101.8 (16.5)	101.4	
Age at menarche (years)				0.116			0.378			0.239
<13	591 (31.2)	78.3 (13.6)	78.3		1,562 (27.0)	1,562		101.4 (15.6)	101.4	
13–14	771 (40.7)	77.3 (14.4)	77.4		1,560 (28.5)	1,560		100.4 (16.6)	100.4	
15	231 (12.2)	76.9 (13.7)	76.9		1,561 (26.9)	1,561		100.5 (15.7)	100.5	
16+	301 (15.9)	77.0 (13.2)	77.0		1,560 (27.1)	1,560		100.1 (15.5)	100.2	
Live births				0.003			0.000			0.000
None	286 (15.1)	78.0 (13.9)	80.1		1,568 (27.3)	1,568		103.8 (15.9)	104.7	
1+	1,609 (84.9)	77.5 (13.9)	77.1		1,560 (27.5)	1,559		100.1 (16.0)	100.0	
Primary school PA (TIH[b])				0.066			0.003			0.006
1 (0–310)	638 (33.7)	76.9 (13.9)	76.9		1,560 (27.4)	1,559		99.1 (15.9)	99.7	
2 (311–1,118)	600 (31.7)	77.4 (14.2)	77.2		1,560 (28.2)	1,560		100.4 (16.5)	100.2	
3 (1,119–2,582)	485 (25.6)	78.1 (13.4)	78.3		1,562 (27.5)	1,563		101.4 (15.8)	101.8	
4 (2,583–31,579)	172 (9.1)	79.1 (13.9)	78.8		1,564 (26.3)	1,565		102.7 (15.3)	103.0	

Smoking status				0.393*			0.090*		0.147*
Non-smoker	612 (32.3)	78.3 (13.8)	77.7		1,562 (27.9)	1,562		101.6 (16.1)	101.3	
Ex-smoker	138 (7.3)	76.6 (13.6)	75.9		1,556 (27.1)	1,556		98..4 (15.7)	98.2	
Current smoker	1,145 (60.4)	77.3 (13.9)	77.7		1,560 (27.5)	1,560		100.5 (16.0)	100.6	
Alcohol drinking status				0.948*			0.850*			0.878*
Non-drinker	998 (52.7)	77.6 (13.7)	77.5		1,561 (27.2)	1,561		100.8 (15.9)	100.7	
Past drinker	210 (11.1)	78.0 (14.6)	77.8		1,560 (28.8)	1,562		100.7 (16.8)	101.2	
Current drinker	687 (36.3)	77.3 (13.9)	77.5		1,561 (27.7)	1,560		100.6 (16.0)	100.5	
Quartile of calcium intake (weekly servings)				0.156			0.401			0.276
1 (0–5.25)	359 (18.9)	76.8 (13.2)	77.0		1,560 (27.3)	1,560		99.9 (15.6)	100.1	
2 (5.3–10.75)	401 (21.2)	77.2 (13.9)	77.2		1,561 (27.7)	1,561		100.8 (16.1)	100.7	
3 (10.8–15.25)	615 (32.5)	77.5 (13.9)	77.5		1,560 (27.7)	1,560		100.3 (16.0)	100.4	
4 (15.3–50.25)	520 (27.4)	78.4 (14.3)	78.2		1,562 (27.7)	1,562		101.6 (16.2)	101.4	

*p value for difference between groups using multivariate analysis of variance

[a] Control for age, BMI, height, education, age at menarche, number of live births, alcohol use, cigarette smoking, physical activity level at primary school, and calcium intake

[b] Total impact hours

increasing BMI and non-significantly with increasing QUI. There was no clear trend for SOS. Both SOS and QUI decreased as height increased, with a similar but weaker trend for BUA. All three QUS measures were significantly lower in parous compared to nulliparous women. All measures also decreased with increasing age at menarche, but none of the trends was significant. In addition, BUA, SOS, and QUI were all significantly and positively associated with primary school physical activity. There was a weak association of decreased SOS with smoking. No associations were found with education level, alcohol intake, or calcium intake.

Further analyses stratified according to three levels of BMI did not reveal any differences in the associations between the QUS measures and height within any of the strata as compared with the original non-stratified analysis. Similar investigations into the associations with age at menarche and physical activity within strata of BMI did not reveal consistent relationships with the adjusted means for any of the QUS measures.

Discussion

In our study, age was associated with BUA, and less strongly with SOS, in both black and mixed-race women. BMI was also associated with BUA in both ethnic groups and with SOS in black women. Height was inversely associated with SOS in both groups. In black women, age at menarche was inversely associated with SOS and more weakly with BUA; associations in mixed-race women were in the same direction but not significant. In both groups, being parous was associated with lower SOS and in both groups QUS measurements were in the direction of greater values for women who had more weight-bearing exercise in primary school. Associations with smoking and alcohol use were weak.

The associated factors found in our study are generally similar to those consistently associated with BMD as measured by DXA in pre-menopausal women [5]. In their review, Tudor-Locke and McColl found associations with BMD to include age, BMI, age at menarche, smoking, load-bearing exercise, and use of depot contraceptive progestins. Additional factors reported to be associated with BMD that our study did not assess were use of calcium supplementation where dietary intake is low, vitamin D levels, primary amenorrhea, and family history of osteoporosis.

Associations with individual risk factors: QUS and DXA

Age

In our study, QUS measures increased with increasing age in black women up to 44 years whereas in women of mixed

race these measures increased up to 39 years and then decreased in the oldest age category. This decrease in the mixed-race women of 40 years and older suggests the onset of bone loss may occur earlier in these women than in black women. The onset of bone loss just prior to menopause has been shown in DXA studies where it is generally reported that peak BMD at the femoral neck had occurred by 20 years of age, whereafter it remained stable until the perimenopausal years when it began to drop. In comparison, total body BMD showed continuous small increments with age [33] possibly due to continued periosteal apposition at the vertebral bodies, with the onset of loss occurring in the late pre-menopausal or in the perimenopausal years [5].

Population differences in the association of bone mass and age may stem from both genetic as well as environmental factors such as physical activity and nutrition [34]. QUS studies on pre- and post-menopausal European [35, 36] and Asian women [37] have shown an increase of both SOS and BUA up to fourth decade followed by a significant decrease after 45 years. Other studies of pre-menopausal women have not consistently reflected changes in QUS with age [13]. This may be due to the relative stability of bone mass prior to menopause as it is generally accepted that the rapid age-related loss of bone with accompanying osteopenia is most apparent in the immediate post-menopausal phase [38]. Alternatively, it may simply reflect the preponderance of cross-sectional over prospective QUS studies.

Body mass index

BUA and SOS increased with increasing BMI in the black women in our study while only BUA increased with increasing BMI in the mixed-race women. We therefore interpret these results cautiously as supporting a general positive association between BMI and QUS measures. BMI has been found to be consistently associated with bone mineral measurements by DXA [5], but QUS associations with BMI have not been as consistent. Positive associations of BUA and SOS with BMI have been demonstrated in different pre-menopausal populations including European women [9, 12], Arabian women [39], and white and African-American women [13, 38]. However, the multicenter European OPUS study [40], the ESOPO study of Italian women [35], and studies of Turkish women [18] did not find a significant association of QUS measures with BMI. In these studies, weight rather than BMI was associated with some but not all QUS measures. Since the main association of body mass with QUS measures reflect lean body mass rather than fat mass [12, 13] and as lean body mass and fat mass affect bone mineral unequally, the association of weight or BMI with QUS measures could be expected to be somewhat inconsistent.

Height

In black and mixed-race women in our study, height was inversely related to SOS but there was no association with BUA. BMI did not explain the associations. In South East Asian women in the USA, estimated BMD from QUS measures was inversely associated with height [41]. However, other studies of DXA and QUS with height have not supported an inverse association. In particular, height was positively and significantly related to BMD at the femoral neck as measured by DXA, but not at the lumbar spine [42]. Some QUS studies have shown positive associations between height and both BUA and SOS [38]; but among Asian pre-menopausal women, increased height was associated only with increased SOS and not with BUA [37].

Age at menarche

The association of increased QUS measures with earlier onset of menarche was present in black women in our study, with weaker associations among mixed-race women. Stratified analysis according to three BMI strata did not alter these findings. A number of cross-sectional DXA studies of pre-menopausal women found an inverse relationship with age at menarche [5]. Increased bone mass associated with early onset of menarche may be attributed to the trophic effect on bone due to longer exposure to estrogens. However, later age at menarche may also be the result of underlying and unreported hormonal irregularities. In these cases, bone mineral would be directly influenced to a greater extent than would otherwise occur in the normal hormonal environment. In some of the European studies [9], the inverse association with age at menarche was present for all three QUS measures, while other European and Saudi Arabian studies showed associations with BUA but not with SOS and QUI [35, 39]. In Asian Americans [41], no relationship was demonstrated.

Parity

Mixed-race parous women in our study had lower BUA and SOS values than nulliparous women. For parous black participants, SOS was lower but not BUA. There is currently no consistent evidence that parity is associated with reduced BMD as measured by DXA [5].

During pregnancy, estrogen levels rise and then decrease postpartum and during prolonged lactation. These variations will affect BMD accordingly [43]. Some QUS studies have found inverse associations of parity with QUI [35], while others have shown inverse associations with SOS but not with BUA [37, 39].

Physical activity

Our study demonstrated a positive association for primary school physical activity measured in total impact hours with QUS measures in mixed-race women. The associations were in the same direction but weaker in black women. It has been shown that high impact in physical activity is a determining factor for increasing bone mass [44] which could explain our results as black women participated largely in activities with normal impact such as walking.

The benefits of current high-impact endurance activities on BMD determined by DXA have been repeatedly demonstrated [5], but the evidence for associations between BMD and historical activity is inconclusive. Historical physical activity is notoriously difficult to capture accurately due to problems with recall. Difficulties in cross-sectional studies also stem from indistinct definitions of current versus historical activity as well as the use of a plethora of different methods for quantifying physical activity. The instrument used to quantify and evaluate historic physical activity in a study population needs to be appropriate to the environment of the participants. Our study reported on a specific range of physical activities during primary school years in a defined way. We were guided by a previous study of South African black and mixed-race women, where the physical activities shown to be most strongly associated with BMD were walking, walking with loads, and sport activities [29]. The positive effect of current physical activity on BUA and SOS has been demonstrated in South African white women [34] and pre-menopausal European, Asian, and American women [9, 13, 37, 38]. However, for historic physical activity, some researchers have shown a relationship with QUS measures [35, 37] while others have not [34].

Comparison of QUS measures in black and mixed-race women

The QUS measures were generally lower among mixed-race women than in the black women in our study. Different QUS machines were used for the two groups. We measured differences between the two machines on three occasions in the course of our study, and analysis of this combined data showed no significant differences between the two machines for BUA, but significantly higher SOS readings for the device used for mixed-race women. Therefore, differences in the machines could not have accounted for the lower QUS values that we observed for mixed-race women.

Data on differences in QUS measures for South African ethnic groups are limited, although there are more results for DXA measurements. All studies suggested that population differences were present. Thus, South African black and mixed-race children under the age of 12 had higher QUS measures than white children [45]. DXA measurements for South African women showed higher femoral BMD in black women than white women [24] and pre-pubertal South African mixed-race children had higher BMC than did black children, while the lowest measures were observed in white children [21, 22].

Strengths and limitations of the study

A major strength of this study was the large sample size. This allowed for high statistical power in the multivariable analyses, which controlled the risk factors of interest for each other as well as for other confounders. The inclusion of two racial/ethnic groups allowed for assessment of consistency of associations in the two populations. In addition, careful QC monitoring and interviewer training contributed to high levels of precision in the study. We were not able to carry out DXA measurements on our study subjects to confirm our results due to distance from study centers with a DXA machine and the expense that this would have incurred. Another limitation is the lack of age data for the various school epochs that we used to classify periods of physical activity. Since bone responses to physical activity are greatest during the growth phase, and as the age during which our participants attended primary school was very variable, information on age finishing primary school might have been useful in allowing us to link historical physical activity to biological age.

Conclusion

This study examined QUS measures in a large population of South African black and mixed-race pre-menopausal women in relation to known risk factors for BMD as measured by DXA. For the most part, associations with risk factors were similar for both study groups. Black women had higher QUS values than mixed-race women after adjusting for confounders. There were some differences between the study groups for the associations of QUS measures with risk factors. In general, however, measures in this study had similar associations to those shown in DXA studies on pre-menopausal women and to those reported in QUS studies in other populations.

In resource-poor settings, QUS may be considered a suitable tool to assess bone characteristics in large epidemiological studies.

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