



Large Bone not Necessarily High Bone Mineral Density: Evidence from a National Survey

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Abstract

There is scarcity of population-level data on the bone areal size (BA) that produces the highest bone mineral density (BMD), and how BA relates to BMD among racial groups. We use population-level data to estimate the BA that coincide with the highest BMD among racial groups in the United States. A total of 7425 participants, age 18–75 years, whose BA and BMD were measured in the United States National Health and Nutrition Examination Survey (NHANES) 2009–2014, were assessed in this study. Multiple regression models were used to estimate race-specific relationships between BA and BMD. The critical BA that associates with the highest (peak) BMD among racial groups adjusted for confounders was estimated. Results showed a curvilinear relationship between BA and BMD at the population level such that BMD increases with BA at lower values and then decreases after a peak value. Races combined, BA of about 45 cm² seems to correspond to a peak femur BMD in this sample. The peak BMD was different among racial groups. The BA at which BMD peaks was lower among blacks and Mexicans compared to whites. We conclude that femur BMD increases up to a critical femur BA and then decreases thereafter. Persons with femur BA at or close to the critical value may tend to have higher than average BMD.

Keywords Bone mineral density · Critical bone size · Femur bone areal size · Peak bone mineral density · Race bone mineral density

Introduction

Information on how bone mineral density (BMD) drifts with bone areal size (BA) is scarce. It had been reported that about 12.6% of the variation in BMD could be attributed to BA [1]. If BA influences BMD, but BMD is a strong indicator of osteoporotic fracture risk, then it is worth estimating which BA is associated with the highest BMD among ethnic groups [1]. There are significant inequality in BMD, bone mineral content (BMC), and BA between racial groups. In fact, even though blacks and Mexicans tend to have smaller BA than whites, they tend to have higher BMD than whites. Several studies have examined the racial differences in BMD, vitamin D, calcium, and parathyroid hormone levels, but there is little evidence to suggest that the relationship between BMD and BA has been examined at the population level [2–4]. Evidently, many other factors

predict BMD which require any analysis of the relationships between BA and BMD be adjusted for such predictors. Factors of particular interest are age, body mass index, gender, and ethnicity [5, 6]. It may be worthwhile to examine how BA or body frame size may influences BMD, and hence fracture risk within racial groups [1, 5–9]. The currently high prevalence of osteoporosis-associated bone fractures, and other related osteomalacia warrant this study [9]. Even though the prevalence of osteoporosis in year 2010 in the United States was high, 16.4% overall, being 5.7% in men and 25.1% in women, the racial inequity was evident, being 10.5% among blacks, 15.6% among whites, and 25.1% among Mexican Americans [9]. Osteoporotic fractures result in untoward personal burden and health care costs that exceed other major adult onset diseases such as cardiovascular disease, breast cancer, and diabetes mellitus [7]. Population-level research that emphasizes racial differences could contribute important information in the effort to alleviate the persistent racial disparity in osteoporosis rates. In this study, we examine the relationship between BMD and BA at the population level to discern any trends generally, and within racial groups. It has been reported that femur BMD

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tends to closely approximate whole-body BMD and it is one of the most frequently assessed due to easy accessibility and convenience [4, 10, 11]. Quantitative information on the BA that corresponds to a peak femur BMD for each racial group is presented.

Methods

Sources of Data and Study Sample

The laboratory datasets from the Mobile Examination Center (MEC) component of the United States National Health and Nutrition Examination Survey (NHANES) 2009–2010 and 2013–2014, updated in October 2015, were analyzed for this study [12]. The NHANES uses a complex multi-stage probability cluster design [13]. It is largely a cross-sectional survey conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), to monitor the health status of the United States civilian population [13]. A total of 7,425 participants were included in the study after satisfying inclusion criteria: had data on age, BA, BMD, BMI, ethnicity, and gender. They comprised 3,732 men and 3,693 women. The final sample comprised 75.5% whites, 13.5% Mexican Americans and other Hispanics, and 11.0% blacks. Participants' data on body weight and height, BMD, BA, BMC, serum vitamin D concentration, and socio-demographic information were accessed from their respective NHANES data files [13]. All NHANES data released for public use have been deidentified. Participants aged 18–75 y were included in the study to improve generalizability of study findings among adults [14]. The Research Ethics Review Board of the National Center for Health Statistics approved the survey procedures and obtained informed consent from all participants [15].

Assigning Racial Affiliation

The NHANES 2009–2014 demographic data files contained self-reported race/ethnicity data which were used to identify participants' racial affiliation [13]. Participants were categorized into one of three racial groups if they identified themselves as such: (1) Non-Hispanic blacks (blacks), (2) Mexican Americans and other Hispanics (Mexicans), and (3) Non-Hispanic whites (whites). Racial groups whose sample sizes were inadequate for classification were included in the white non-Hispanic group.

Assessing Bone Mineral Density, Bone Mineral Content, and Total Femur Bone Area

Because subregional BMD tends to closely approximate whole-body BMD, total femur BMD was assessed in this

study, especially due to ease of accessibility and reliability [3, 4, 9–11, 16]. Total femur scans were performed to determine total femur BMD, total femur BMC, and total femur BA using dual energy X-ray absorptiometry (DXA) [16]. A Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts) with a Hologic Discovery software version 12.4 was used [16]. The DXA scans were performed on the left side of the body by trained and certified radiology specialists [4, 16]. Further details on the DXA scan protocols are documented in the body composition procedures manual located at <https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/2013_Body_Composition_DXA.pdf>. Compared to other radiation-based techniques, DXA is favored for the assessment of bone and other skeletal traits because of its specificity, speed, low radiation, and safety [17, 18].

Exploring the Relationship Between Bone Areal Size and Bone Mineral Density

Locally weighted estimated scatterplot smoothing (LOWESS) was used to display relationships between BMD and BA generally, and by race [4, 19]. LOWESS is a robust non-parametric method for visualizing the relationship between two continuous variables, in this case, between BA and BMD without the concerns about *a priori* statistical assumptions [4, 19]. The purpose of using LOWESS is to examine how BMD values trend with BA values in a population-level cross-sectional data.

Multivariable regression models were used to estimate BA values (critical BA) that coincide with the highest (peak) BMD values among racial groups. The LOWESS analysis indicated a curvilinear relationship between BA and BMD so we included a quadratic term for BA in the multiple regression analysis. In this study, critical BA values were calculated from first- and second-order derivatives using the respective coefficients of the variables in the race-specific multivariable regression models. For instance in white men, BMD is related to BA such that $BMD = [0.4251 + 0.0153BA - 0.00014BA^2 - 0.0025age + 0.0111BMI]$. Accordingly, the first-order derivative of BMD with respect to BA is $\frac{\partial BMD}{\partial BA} = 0.0153 - 0.00028BA$, and the second-order derivative is $\frac{\partial^2 BMD}{\partial BA^2} = -0.00028$. So that $BA = \frac{\partial BMD}{\partial BA} = 0.0153 - 0.00028BA = 0$ will give the value of BA that generates the peak value of BMD. In order to estimate the average peak BMD at the critical BA for each racial group, we used the person at the group weighted average age and group weighted average BMI as the referent.

To enable weighting per the MEC sampling weights during data analysis, STATA version 14.0 (STATA Corporation, College Station, TX) was used to estimate all descriptive and inferential statistics [20]. Gender-stratified estimates of averages for serum 25(OH)D concentration, age, BMI, BA, BMC, and BMD were done to enable unbiased assessment

of BMD-related background characteristics across racial groups. To promote reliable estimation of differences in BA, BMC, and BMD between racial groups, the following potential confounding variables were controlled in multivariable regression models: age, BMI, education, income, marital status, and upper leg length (ULL). The categorical confounding variables education, income, and marital status were examined as indicator variables. All analyses were stratified by race and by gender where gender-stratified analysis yielded a different outcome. Whites were the referent in the multivariable regression analysis. Significant differences between racial groups were tested using the native *t* test component of the multivariable regression models. In all analyses, statistical differences were deemed significant at $p < 0.05$.

Results

The background characteristics of the study sample related to BMD are shown in Table 1. Similar to the findings of other studies, the average serum vitamin D concentration of whites was higher than for both blacks and Mexicans, whereas the BMD of blacks and Mexicans were higher than for whites, $p < 0.001$ [3–5]. After adjusting for age, BMI,

income, education, marital status, and ULL, the BA values of blacks and Mexicans were about 2 cm^2 less than the femur BA of whites, all $p < 0.001$ (Table 2). Genders combined, femur BA significantly correlated with femur BMD, $r = +0.30$, $p < 0.001$. On average, black men had about 1.5 greater BMC than whites, whereas black women and Mexican women had similar BMC to white women (Table 2).

The scatter plots of BA versus BMD, and BA versus BMC at the population level are depicted in Fig. 1a, b, respectively. A keen observation of Fig. 1 may show that the relation between BA and BMD appear non-linear, whereas that between BA and BMC appeared quite linear. Among the racial groups, the relationship between femur BA and femur BMD was curvilinear such that femur BMD increases with increasing femur BA up to a peak value and then decreases after a critical femur BA value (Fig. 2a, b). Racial groups combined, it seems femur BA of about 45 cm^2 associates with highest femur BMD. Even though similar patterns were observed, the femur BA (critical femur BA) that associated with the highest BMD differed among the racial groups. Whites had the largest critical femur BA followed by blacks, with Mexicans having the least (Fig. 3). The overall trend shows clear disparity in the magnitudes of femur BA and femur BMD among the ethnic groups. The peak femur BMD was lowest for whites, followed by Mexicans, with blacks having the highest value.

Table 1 Background characteristics of participants by racial group

	<i>n</i>	Blacks	<i>n</i>	Mexicans	<i>n</i>	White ^a	<i>n</i>	Total population
Age (years)								
Men	722	45.9 ± 0.7 ^{b*}	1062	42.8 ± 0.6*	1948	48.9 ± 0.4	3732	47.8 ± 0.3
Women	643	45.8 ± 0.8*	1069	43.8 ± 0.8*	1981	49.2 ± 0.2	3693	48.1 ± 0.6
Body mass index (kg/m ²)								
Men	722	29.3 ± 0.3*	1062	29.0 ± 0.2	1948	28.7 ± 0.2	3732	28.8 ± 0.2
Women	643	32.3 ± 0.4*	1069	29.8 ± 0.2*	1981	28.2 ± 0.2	3693	28.9 ± 0.2
Upper leg length (cm)								
Men	722	42.3 ± 0.1*	1062	39.4 ± 0.2*	1948	41.1 ± 0.1	3732	41.0 ± 0.1
Women	643	38.7 ± 0.2*	1069	35.2 ± 0.2*	1981	37.1 ± 0.1	3693	37.0 ± 0.1
Serum vitamin D (ng/L)								
Men	487	18.9 ± 1.0*	796	23.3 ± 0.6*	1359	28.6 ± 0.5	2642	26.8 ± 5
Women	498	19.0 ± 0.8*	881	22.3 ± 0.6*	1428	31.1 ± 0.6	2803	28.4 ± 5
Total femur bone areal size (cm ²)								
Men	722	41.1 ± 0.4*	1062	40.4 ± 0.2*	1948	42.7 ± 0.1	3732	42.2 ± 0.1
Women	643	31.9 ± 0.1*	1069	30.8 ± 0.1*	1981	33.0 ± 0.1	3693	32.6 ± 0.1
Total femur bone mineral density (g/cm ²)								
Men	722	1.10 ± 0.01*	1062	1.04 ± 0.01*	1948	1.02 ± 0.01	3732	1.03 ± 0.01
Women	643	1.00 ± 0.01*	1069	0.94 ± 0.01*	1981	0.90 ± 0.01	3693	0.92 ± 0.01
Total femur bone mineral content (g)								
Men	722	45.5 ± 0.6*	1062	42.2 ± 0.3	1948	43.4 ± 0.4	3732	43.5 ± 0.1
Women	643	31.7 ± 0.3	1069	28.9 ± 0.2	1981	29.8 ± 0.2	3693	29.9 ± 0.2

^aThe white racial group was the referent

^bValues are mean ± SE weighted per NHANES Mobile Examination Center sampling weights

* Significantly different from the referent, $p < 0.05$

Table 2 Race-specific differences in bone mineral content, bone mineral density, and bone areal size partitioned by gender

Measure	Blacks ^a <i>n</i> = 1365			Mexicans and Hispanics <i>n</i> = 2131		
	<i>n</i>	β coefficient ^b	<i>p</i> value	<i>n</i>	β coefficient	<i>p</i> value
Total femur bone areal size (cm ²)						
Men	722	-1.8 (-2.3, -1.4)	0.001*	1062	-0.6 (-1.0, -0.3)	0.001*
Women	643	-2.0 (-2.3, -1.8)	0.001*	1069	-1.1 (-1.3, -0.8)	0.001*
Total femur bone mineral density (g/cm ²)						
Men	722	0.09 (0.08, 0.10)	0.001*	1062	0.04 (0.04, 0.07)	0.001*
Women	643	0.06 (0.04, 0.07)	0.001*	1069	0.03 (0.02, 0.04)	0.001*
Total femur bone mineral content (g)						
Men	722	1.5 (0.6, 2.5)	0.003*	1062	0.4 (-0.4, 1.1)	0.286
Women	643	-0.1 (-0.7, 0.4)	0.612	1069	-0.4 (-0.8, 0.0)	0.056

^aThe white racial group was the referent

^b β -coefficients have been adjusted for age, BMI, income, education, marital status, and ULL. The NHANES Mobile Examination Center sampling weights were applied. Values in parenthesis are 95% confidence intervals

* Variables with $p < 0.05$ are significantly different from the referent

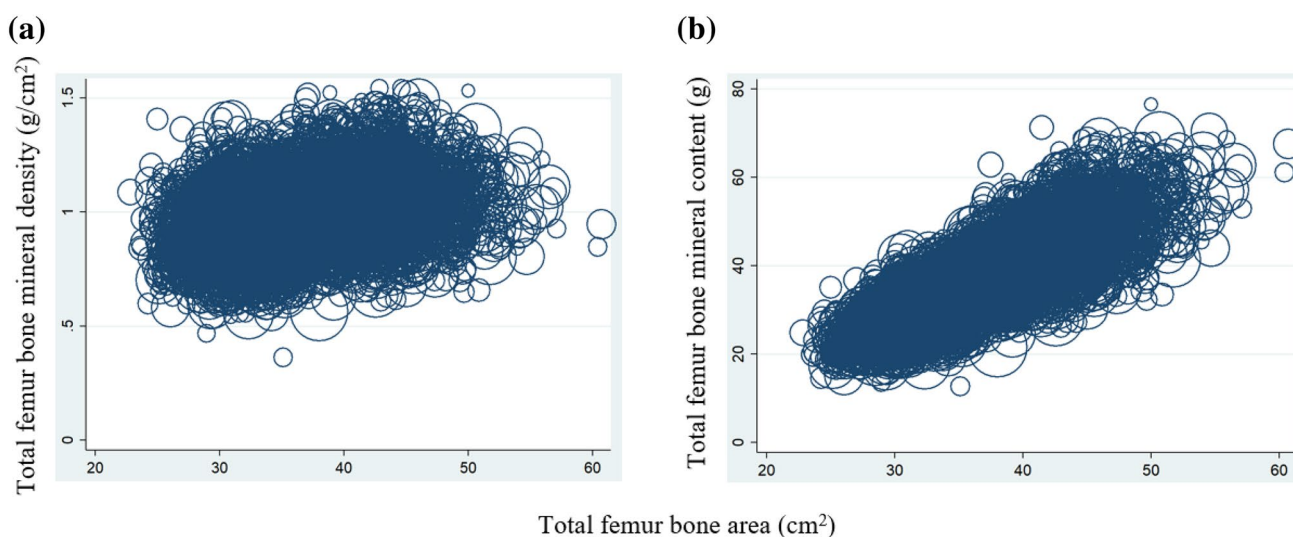


Fig. 1 Scatter plots of total femur bone area against total femur bone mineral density (a) and total femur bone mineral content (b). Plots are weighted, shown by the sizes of the bubbles, per the NHANES Mobile Examination Center sampling weights

Mexicans had the lowest critical femur BA but did not have the lowest femur BMD. Whites had the largest critical femur BA but had the lowest femur BMD. Even though blacks had the highest femur BMD, they did not have the highest critical femur BA. Unlike femur BMD, BMC increased almost linearly with increasing BA (Fig. 2c, d).

Discussions

Using population-level data, we show that within racial groups, femur BMD increases with increasing femur BA up to a peak value and then decreases as femur BA increases

further. This curvilinear relationship between BMD and BA suggests a critical value of BA beyond which further increase in BA does not associate with proportionate increase in BMD [1]. In other words, BMC per square area thins out at large BA. Since BMD is BMC standardized for BA, a linear relationship between BA and BMD is expected. The curvilinear relationship could indicate that the correction for BA fails. However, it is unlikely that the observed relationship is artifactual at the population level. We interpret the curvilinear relationship to mean that BMD could be lower than expected in persons who have small or overly large BA. The observed relationship between BA and BMD could have implications for bone fracture risk since low

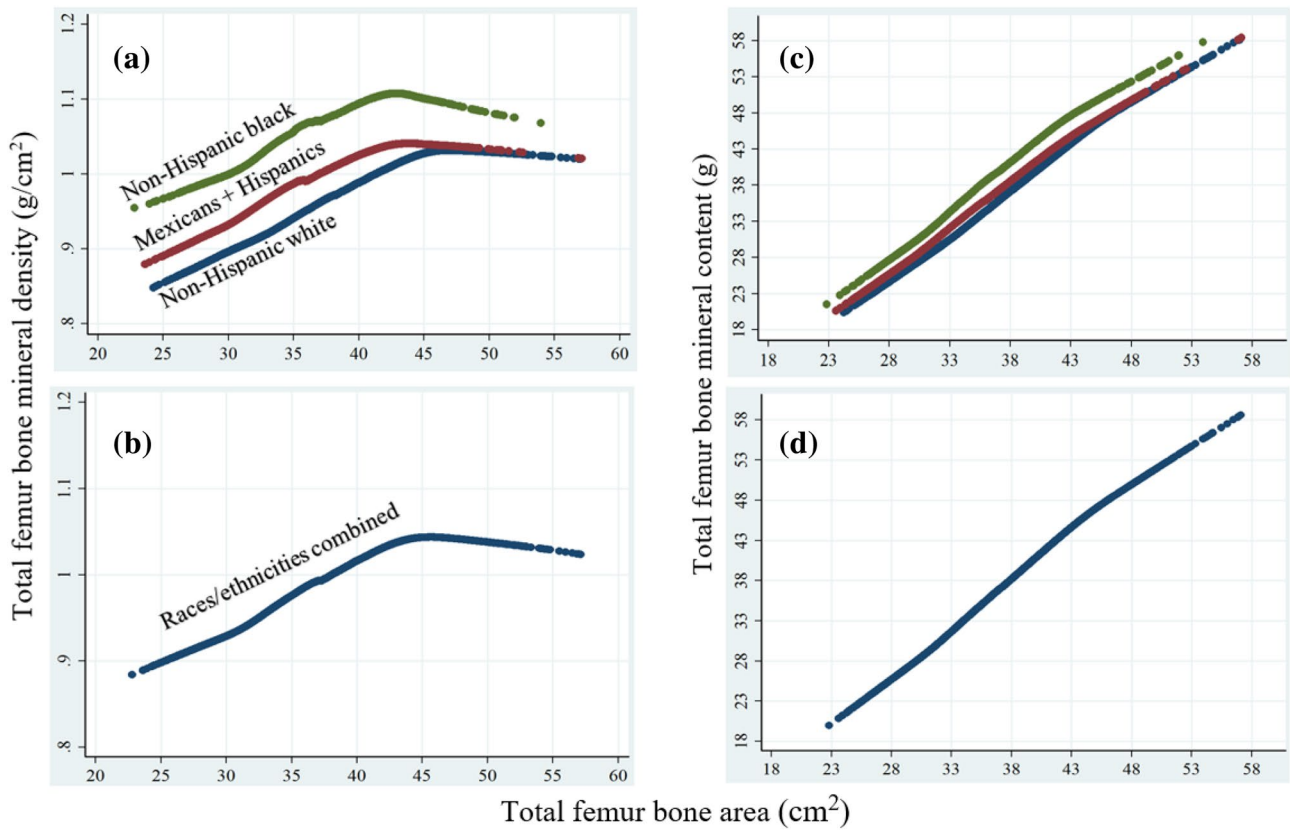


Fig. 2 LOWESS regression plot showing total femur bone mineral density as a function of total femur bone areal size categorized by race. LOWESS analysis indicated a curvilinear relationship between BA and BMD so we used multiple regression with a quadratic term for BA. Chart (a) shows the relationship between BA and BMD. Non-Hispanic whites include other racial and multiracial groups whose

sample sizes were inadequate for categorization. Chart (b) shows the relationship between BA and BMD for all races combined. The plots in charts (c, d) follow the same order and labeling as for charts (a, b). LOWESS is the acronym for locally weighted estimated scatterplot smoothing [5, 19]

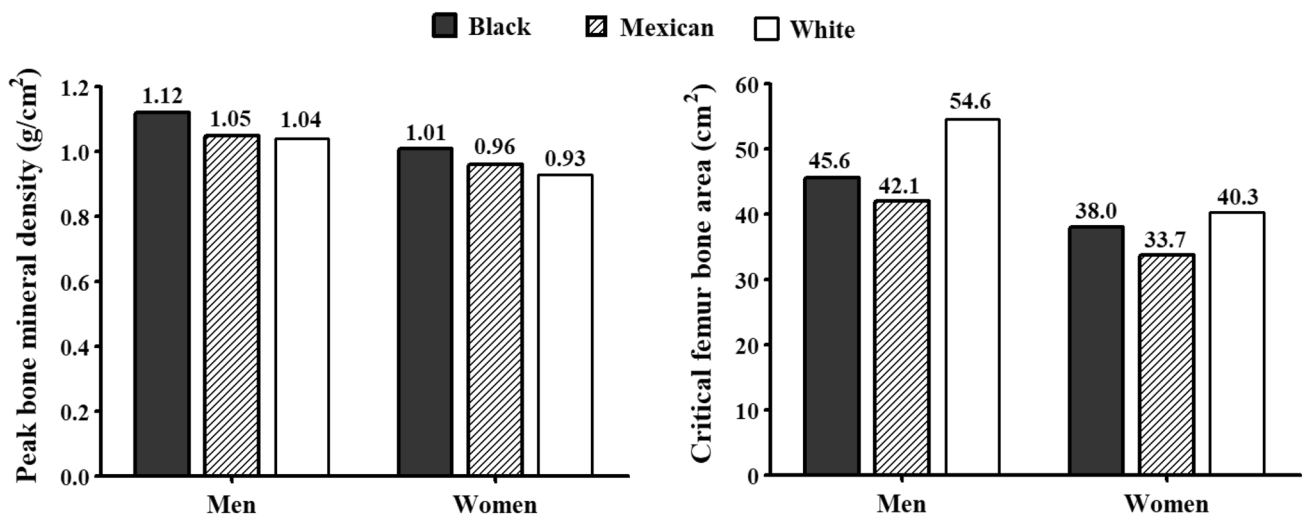


Fig. 3 Peak femur bone mineral density and critical femur bone areal size categorized by gender and by ethnicity. White represents non-Hispanic whites including other racial and multiracial groups whose sample sizes were inadequate for partitioning. Mexican include other Hispanics

BMD is a strong predictor of bone fracture [1, 21]. It is probable that persons who have BA close to or at the critical value would associate with high BMD. Even though there appears to be some evidence to support BA as an important factor in bone fracture incidence, evidence is rather strong for a relationship between BMD and fracture risk [1, 21–23]. There is some indication, however, that small BA associates with osteoporosis diagnosis and increased risk of bone fracture [22]. Bone size is an independent determinant of bone strength and bone fracture [1, 21, 22].

In the present study, we observed that the BA to attain the peak BMD is smallest for Mexicans, intermediate for blacks, and largest for whites. Thus, to attain the peak BMD, whites may need much larger BA which, obviously, will require a larger skeletal growth. Mexicans had lowest BMC and smallest BA which is a recipe for low BMD and risk of bone fracture [23]. This could offer one more reason for the high prevalence of osteoporosis among Mexican Americans which was 25.1% compared to 15.6% among whites, and 10.5% among blacks in year 2010 [9].

Fig. 3 shows that between the racial groups, a large BA did not coincide with a greater peak BMD value. Even though BMD was higher among blacks and Mexicans than whites, the reverse was true for BA which was largest among whites. Blacks associated with smaller BA but higher BMC compared to whites. A consequence of this discrepancy is amplification of BMD in blacks based on the definition of BMD. This could be another reason why blacks associate with higher BMD than other races irrespective of the lower vitamin D nutritional status [4, 24–27]. Other reasons for this discrepancy include early suppression of parathyroid hormone which may obviate the effects of the lower vitamin D nutritional status on BMD and BMC, and the fact that dietary calcium intake and level of physical activity may not significantly influence BMD in blacks [4, 27]. Given equal rate of bone mineralization in humans, it can be seen why large BA in whites could attenuate BMD, whereas small BA in blacks and Mexicans could accentuate BMD. Even though poor early growth is associated with decreased BMC in adulthood, it does not alter BMD [23]. In an earlier study, Deng et al hinted that some of the variation in BMD was attributable to BMC and BA [1]. Knowledge of these associations, as observed in the present study, could be helpful to bone fracture prevention efforts, bone health maintenance, and efforts to attain optimum BMD. In this study, we provide evidence that different femur BAs associate with different BMD. Further studies need to focus on whole-body BMD analysis, and assessment of bone fracture risk among small and overly large frame persons.

A strength of this study is the race-specific analyses which may have precluded biological confounding including racial disparities in vitamin D levels, vitamin D receptors sensitivities, parathyroid hormone levels, and frame size [2–4]. Some

limitations in this study are worth mentioning. The measurements of BA and BMC were made on wide-angle Hologic fan-beam DXA scanners, the sensitivity of which may be affected by obesity. However, BMI was controlled during the regression analysis to alleviate this effect. In addition, this technical issue does not affect the calculated BMD as it cancels out in the end. In the NHANES, trained personnel do the DXA scans while applying relevant precautionary and quality control measures. Like other cross-sectional studies, not all possible confounding variables might have been controlled. Therefore any applications of the outcomes of this study should be done with the usual precautionary steps associated with the use of cross-sectional data. Despite these limitations, this study provides credible and strong evidence that BA may influence BMD, and for each racial group there is a critical BA beyond which BMD thin out.

In conclusion, within each ethnicity, BMD increases up to a critical BA and then decreases thereafter. Blacks and Mexicans have less BA, higher BMD, and lower critical BA compared to whites. Individuals with BA at or close to the critical value may associate with higher than average BMD.

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Compliance with Ethical Standards

Conflict of interest Francis Tayie and Chen Wu have no conflict of interest regarding this article publication.

Human and Animal Rights and Informed Consent The Research Ethics Review Board of the National Center for Health Statistics approved the survey procedures and obtained informed consent from all participants.

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