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Genetic admixture and body composition in Puerto Rican adults from the Boston Puerto Rican Osteoporosis Study

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Abstract

Population admixture plays a role in the risk of chronic conditions that are related to body composition; however, our understanding of these associations in Puerto Ricans, a population characterized by multiple ancestries, is limited. This study investigated the relationship between genetic admixture and body composition in 652 Puerto Ricans from the Boston Puerto Rican Osteoporosis Study. Genetic ancestry was estimated from 100 ancestry-informative markers. Body composition measures were obtained from dual-energy X-ray absorptiometry. Multivariable linear regression analyses examined associations between bone mineral density (BMD) of the hip and lumbar spine and percent fat mass and lean mass with genetic admixture. In Puerto Ricans living on the US mainland, European ancestry was associated with lower BMD at the trochanter (P = 0.039) and femoral neck (P = 0.01), and Native American ancestry was associated with lower BMD of the trochanter (P = 0.04). African ancestry was associated with a higher BMD at the trochanter (P = 0.004) and femoral neck (P = 0.001). Ancestry was not associated with percent fat mass or lean mass or waist circumference. Our findings are consistent with existing research demonstrating inverse associations between European and Native American ancestries and BMD and positive relationships between African ancestry and BMD. This work contributes to our understanding of the high prevalence of chronic disease experienced by this population and has implications for other ethnic minority groups, particularly those with multiple ancestries. Future research should consider interactions between ancestry and environmental factors, as this may provide individualized approaches for disease prevention.

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Compliance with ethical standards

Conflict of interest: All authors have no conflicts of interest.

Keywords

Genetics; Race/ethnicity; Aging; Dual-energy X-ray absorptiometry

Introduction

Hispanics have been shown to have a higher prevalence of chronic diseases (or age-related conditions) compared with non-Hispanic whites, which may, in part, be related to obesity and more specifically to body composition [1]. Disparities also exist among Hispanic subgroups, with Puerto Ricans having the highest prevalence of obesity compared with the other subgroups [2]. According to recent results from the Community Health Study/Study of Latinos (HCHS/SOL), the prevalence of obesity ranged from 27 % in South American men to 41 % in Puerto Rican men and from 31 % in South American women to 51 % in Puerto Rican women aged 18–74 years [2]. While links between adiposity and cardio-metabolic disease have been established, evidence for a role of adiposity in other chronic diseases, such as osteoporosis, has emerged only more recently [3]. Contrary to popular belief, Hispanics have been found to have similar [4–6] and, according to recent national estimates, perhaps higher prevalence [7] of osteoporosis than non-Hispanic whites. There is evidence that variation in bone status also exists among Hispanic subgroups [8]. The majority of studies on bone health have been conducted in Mexican Americans; however, preliminary data from the Boston Puerto Rican Osteoporosis Study indicate that Puerto Rican older adults, particularly men, are at increased risk for osteoporosis compared with Mexican Americans (unpublished data). Identifying contributing factors to the variation in body composition, including bone measures, is necessary for understanding and developing strategies for reducing health disparities experienced by this population.

Population admixture quantifies the genomic contribution of individuals from multiple ancestral origins due to the history of inter-marriage between ethnic populations. Population admixture has been shown be associated with risk of disease [9–11] and may play an important role in chronic conditions that are related to body composition [11]. A few studies have examined the association between genetic ancestry and measures of body composition, such as bone mineral density (BMD) [12–14]. Others have studied associations between ancestry and fat mass [12, 14, 15], lean body mass [12], body mass index (BMI) [14–17] and waist-to-hip ratio (WHR) [16]. Our understanding of these relationships in multi-ancestral groups, such as Puerto Ricans, is limited. The genome of each Puerto Rican consists of continuum admixture of three ancestral origins: Southern European, West African and Native American. To our knowledge, only one small study ($n = 64$) examined the relationship between genetic admixture and body composition phenotypes, including BMD, in a Puerto Rican population [14]. That study found a significant inverse association between BMD and European admixture ($R^2 = 0.065$, $P = 0.042$); however, no association was found between adiposity measures and admixture.

In light of the substantial gaps in understanding of sources of health disparities in Puerto Rican adults, the Boston Puerto Rican Osteoporosis Study presents an unusual opportunity to examine the roles of multiple ancestries and multiple body composition phenotypes in a

single group. The primary objective of this study was to examine the relationship between Southern European, West African and Native American ancestries and body composition, including bone and adiposity phenotypes, in Puerto Rican adults.

Materials and methods

Study population

This study includes 652 Puerto Rican adults from the Boston Puerto Rican Osteoporosis Study (BPROS) with complete body composition measures from dual-energy X-ray absorptiometry (DXA) and for whom DNA samples were available. The BPROS is an ancillary study to the Boston Puerto Rican Health Study (BPRHS), a population-based prospective study of Puerto Rican adults, aged 45–75 years, residing in the Greater Boston area [18]. Baseline recruitment occurred between 2004 and 2009. Briefly, areas of high Hispanic density in the Boston metropolitan area were identified from the year 2000 Census, and households with at least one Puerto Rican adult aged 45–75 years were identified. Only one eligible Puerto Rican adult per household was randomly selected for participation (specifics of the study and recruitment methodology are described in detail elsewhere) [18]. Recruitment occurred through door-to-door enumeration (84 %), community activities (8 %), and referrals from community partners and/or through media or flyers placed in the community (8 %). Exclusion criteria included inability to answer questions due to serious health conditions, plans to move from the Greater Boston area within 2 years and/or a Mini Mental State Examination (MMSE) score ≤10. Baseline and 2-year follow-up interviews were conducted by bilingual interviewers in the participants' homes to collect information on socioeconomic status, health and health behaviors, stress, acculturation and dietary intake. Anthropometric and blood pressure measures were also completed. Blood samples were obtained for analysis of biological markers.

The majority of participants (84 %) completed 2-year follow-up interviews with an average of 2.2 years (SD 1.1) between the baseline and 2-year follow-up visits. Upon completion of the 2-year follow-up interview, participants were invited to join the BPROS. Those who provided written informed consent were scheduled a visit at the Metabolic Research Unit at the Human Nutrition Research Center on Aging (HNRCA) at Tufts University to undergo body composition measures (DXA) and to complete additional measures and questionnaires on osteoporosis medication use and sunlight exposure. All questionnaires were administered by trained bilingual interviewers. Of the 1267 participants who completed the 2-year follow-up interview, 973 participated in the BPROS. Primary reasons for not participating included: (1) not being interested in the study ($n = 205$), scheduling difficulties ($n = 47$), loss to follow-up ($n = 11$), relocation out of Massachusetts ($n = 13$) and other reasons ($n = 2$). Further, 20 participants died before the BPROS visit. Population admixture was estimated for 1005 participants of the 1504 recruited at baseline. From the parent BPRHS study, we used baseline data on sex, age and education level and 2 years of follow-up data on physical activity, waist circumference and dietary intakes. We used height, weight, BMI and anthropometric and body composition measures from the BPROS study. For the current analysis, we included participants with both population admixture and DXA data. A total of 652 out of the 1005 participants with admixture data had DXA data. We conducted power

calculations for BMD and obesity-related traits. For the sample size of 652 with five adjusted covariates, and significance at $P = 0.05$, we had >80 % power to detect an association between ancestry with BMD (total hip, trochanter, femoral neck, lumbar spine or total body) and with obesity-related traits (fat mass, lean mass and waist circumference) for ancestries that account for 1 % or more of the *R*-square of the traits. The Institutional Review Boards (IRB) at Tufts University, Northeastern University and the University of Massachusetts Lowell approved the study.

Measures

Independent measures—Dual-energy X-ray absorptiometry (DXA, GE-Lunar model Prodigy scanner; General Electric) was used to measure BMD (g/cm^2) of the total hip, trochanter, femoral neck and lumbar spine (L2–L4). DXA measures were obtained following standard procedures at the Bone Metabolism Laboratory at the HNRCA, and the right hip was routinely scanned unless the participant reported having a previous hip fracture or joint replacement. In this laboratory, the root mean square precision of BMD measures is as follows: 0.65 % for the total hip, 1.04 % for the lumbar spine and 1.31 % for the femoral neck [19]. The root mean square precision of total fat is 0.94 % and of nonfat soft tissue is 0.77 % [19]. Stability of the measures was assessed by scanning an external standard (aluminum spine phantom: Lunar Radiation Corp.) weekly. Scans with T-scores >4.0 were identified and reviewed by the study endocrinologist at Tufts University (BD-H) to check for non-anatomical parts and for extra-skeletal calcification. We excluded 25 participants' lumbar spine (L2–L4) measures and 7 participants' total hip, trochanter and femoral neck measures. Waist circumference was measured, in duplicate, at the umbilicus using a flexible tape measure.

Outcome measures—Individual genetic ancestry was estimated from 100 ancestry-informative markers (AIMS) that were selected if the difference in the allele frequency was at least 0.5 between any two of the three ancestral populations: West African, European and Native American, as described in detail elsewhere [11]. The 100 AIMS were distributed across the genome and were in linkage equilibrium in the three ancestral populations. DNA was isolated from buffy coats of peripheral blood using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), and AIMS were genotyped using IPLEX protocols for multiplex PCR, single base primer extension and generation of mass spectra [11]. Two programs (STRUCTURE 2.2 [20, 21] and IAE3CI [22, 23]) were used to calculate individual ancestry based on the genotypes of the AIMS in reference to the three ancestral populations (West African, European and Native American) [24].

Other covariates—Age, sex and educational attainment were assessed at baseline through questionnaire. Educational attainment was categorized as <8th grade, 9th–12th grade, and some college or higher. Physical activity was assessed using a questionnaire based on a modified Paffenbarger questionnaire of the Harvard Alumni Activity Survey [25]. A physical activity score, assessed at 2-year follow-up, was calculated by multiplying the total number of hours spent in heavy, moderate, light or sedentary activities over a 24-h period by weighing factors using metabolic equivalents for each of the aforementioned activities (sleeping = 1.0, sitting = 1.1, light = 1.5, moderate = 2.4 and vigorous = 5.0) [25, 26].

Anthropometric data, including height and weight, were obtained from the BPROS visit and were measured in duplicate consistent with the techniques used by the National Health and Nutrition Examination Survey (NHANES). BMI was calculated as weight (kg) divided by height (m^2). Height was measured using a standing stadiometer. Dietary intake, assessed at 2-year follow-up, was measured using a semiquantitative food frequency questionnaire (FFQ) adapted and validated for the Puerto Rican population [27]. Daily average nutrient intakes were calculated using the Nutrition Data System for Research software (Nutrition Coordinating Center, Minneapolis, MN).

Statistical analyses

Data were analyzed using STATA (v 13). Formal hypothesis testing was two-sided with a significance level of *P* value <0.05. Distributions of independent and dependent variables were examined for normality. We checked for normal distribution of residuals from the linear regressions. Multivariable linear regression analyses were used to examine associations between BMD, percent fat mass and percent lean mass with population admixture. For each association, two multivariable models were examined. For BMD and genetic admixture, model 1 was adjusted for age and sex. Model 2 was adjusted for sex, age and BMI. We also examined models adjusted for height, as bone thickness is proportional to height. Models adjusted for physical activity, dietary vitamin D and dietary calcium intake and vitamin D supplementation produced similar results.

For analyses of associations of percent fat mass, percent lean mass and waist circumference with population admixture, model 1 was adjusted for age and sex, and model 2 was adjusted for sex and age, education and height. We included covariates in our models that changed beta estimates by 10 % and/or have been shown in other studies to be potential confounders in these associations [28–31]. For waist circumference only, model 2 was adjusted for education and BMI, as others have suggested that this is a better predictor of intra-abdominal fat mass than waist circumference alone [32]. We also adjusted models for protein intake adjusted for total energy using the residual method [33] and total energy intake, as protein consumption has been associated with changes in body composition [34]; beta coefficients were similar to those in model 2 (data not shown). All models were tested for interactions by sex; no significant interactions were noted; therefore, sex was included in all models as a covariate.

Results

Our analysis included 468 women (72 %) and 184 men (28 %) (Table 1). The mean age was similar for men and women (60.2 ± 7.7 vs. 60.6 ± 7.3, $P = 0.57$). A greater percentage of men had attained a 9th–12th grade education level compared with women (43 vs. 33 %, $P = 0.04$). Men had greater BMD at all hip and spine sites compared with women ($P < 0.001$ for all). Percent body fat was significantly higher among women compared with men (45 vs. 29 %, $P < 0.001$), whereas percent lean body mass was significantly higher among men compared with women (67 vs. 52 %, $P < 0.001$). Women had higher BMI compared with men (33.1 vs. 30.0 kg/m^2, $P < 0.001$). No significant differences by sex were noted for waist circumference. The sample showed higher European ancestry 0.57 (SD = 0.15) and lower

African 0.28 (SD = 0.15) and Native American 0.15 (SD = 0.06) ancestry, with no significant differences by sex.

In models adjusted for age, sex and BMI, European ancestry was significantly associated with lower BMD at the trochanter (β = −0.047; SE = 0.023, P = 0.039) and femoral neck (β = −0.095; SE = 0.037, P = 0.01) (Table 2). African ancestry was associated with higher BMD at the trochanter (β = 0.064; SE = 0.022, P = 0.004) and femoral neck (β = 0.115; SE = 0.036, P = 0.001) after adjusting for sex, age and BMI. Native American ancestry was significantly associated with lower BMD at the trochanter (β = −0.11; SE = 0.054, P = 0.04) and was marginally inversely associated with lower BMD at the lumbar spine (β = −0.22; SE = 0.11, P = 0.074). There was no association between European or African ancestry with the lumbar spine. After adjusting for sex, age, BMI and height in multivariable linear regression analysis, the associations between ancestry and BMD were attenuated to only approach significance (P > 0.074), with the exception of African admixture with the femoral neck, which was attenuated, but remained significant (P = 0.027).

There were no significant associations between European, African or Native American ancestry and percent fat mass, percent lean mass or waist circumference in multivariable linear models adjusted for age and sex (Table 3). Models adjusted for education, height (for percent lean mass and fat mass) and education and BMI (for waist circumference only) remained nonsignificant with additional adjustment.

Discussion

Findings from the current study in a Puerto Rican population extend existing evidence for the role of specific ancestries in bone health. Our analysis of the relationship between ancestral admixture and bone phenotypes demonstrated that European and Native American ancestries were associated with lower BMD at the trochanter and femoral neck (European ancestry only), whereas African ancestry was associated with greater BMD at the trochanter and femoral neck. There were no relationships between admixture and other measures of body composition, including percent body fat, percent lean mass and waist circumference.

Our findings of an association between European ancestry and BMD are consistent with a small study that reported an inverse association between European ancestry and BMD in Puerto Rican adults (R^2 = 0.065, P = 0.042) [14]. In that study, Puerto Rican adults had genetic contributions from European (53.3 ± 2.8 %), West African (29.1 ± 2.3 %) and Native American (17.6 ± 2.4 %) ancestries, which are comparable to the percentages reported in the current study. However, that study found no association between African or Native American admixture and total body BMD, potentially owing to the small number of participants (n = 64). Evaluation of total BMD, rather than BMD at individual sites, was conducted in the earlier study, which may have also influenced their ability to detect associations [14]. In our sample of 652 Puerto Rican adults, we found a significant relationship between European, African and Native American ancestries and BMD of hip sites, particularly the trochanter and femoral neck, suggesting that variation in genes between African, European and Native American populations' contribute to differences in BMD at the hip. Adjusting models for height attenuated associations to non-significance,

with the exception of African admixture and BMD of the femoral neck ($P = 0.027$). Height is estimated at 70–90 % heritable [35]; therefore, adjusting for height may mask the genetic variability associated with population admixture.

Others have reported significant associations between increasing African ancestry and BMD; however, these studies were conducted in African American adults [13], whose African ancestry, on average, is much greater than that of Puerto Ricans. In one study, higher African ancestry was related to higher BMD and bone strength in African American women. However, African American women with higher African ancestry also had a greater rate of bone loss over 6 years, relative to non-Hispanic white women, suggesting that non-genetic factors also play an important role in differences across ethnic groups [13]. In general, however, these findings and ours are consistent with well-known ethnic differences in risk of low bone mass and osteoporosis between African Americans and non-Hispanic whites. National prevalence estimates indicate that non-Hispanic blacks have lower prevalence of osteoporosis and low bone mass compared with non-Hispanic whites [36, 37]. Native American/Alaskan native women, on the other hand, have been shown to have similar BMD to non-Hispanic whites [38].

Similar to our findings, a small study of Puerto Rican adults found no association between ancestry and obesity-phenotypes [14], although ethnic variation in risk of obesity has been documented [1, 2]. A small study of Hispanic and Native American college students found no association between admixture and BMI or percent body fat in Hispanics; however, a small inverse association between European genetic admixture and body composition measures was noted for Native Americans ($n = 15$) [15]. Other studies have also reported associations between genetic ancestry and BMI and other body composition measures [17]. Lins et al. [17] reported a significant correlation between European ancestry and BMI ($r = 0.165$; $P = 0.037$) in a sample of elderly women from Brazil with a combination of European (57.5 %), Native American (25.8 %) and African (16.7 %) ancestries. We did not observe a significant association between Native American ancestry and adiposity, although Native Americans as a group are reported to have greater obesity risk compared to non-Hispanic whites [39]. This apparent discrepancy may be related to the relatively low (~16 % from the table) percentage of Native American ancestry in Puerto Ricans. These results do not suggest a strong ancestral genetic component for obesity. It seems more likely that environmental factors, such as poor dietary quality and physical inactivity, or interactions between genetic and environmental factors may have a stronger impact on obesity in this population. Alternatively, the relatively broad category of ancestry could encompass variants that tend to increase or decrease genetic susceptibility to obesity, with the consequence that the overall association is neutral.

Although the current study focuses on genetic risk, as represented by ancestry rather than individual genetic variants, findings from genome-wide association studies (GWAS) for BMD are informative in identifying potential contributors to ancestral differences. For example, a large GWAS study of premenopausal European-American and African American women identified 50 single-nucleotide polymorphisms (SNPs) for BMD measures at the lumbar spine and femoral neck [40]. Only one top variant reported for European-Americans was replicated in African Americans for the femoral neck, and none were replicated for the

lumbar spine. The failure to demonstrate consistency across ethnic groups may be related to differences in the frequencies of variant alleles or differences in linkage disequilibrium patterns. This highlights the critical importance of examining genetic contributions to disease in groups of diverse ancestral admixture.

Strengths and limitations of this study must be considered. Our cross-sectional design is an important limitation, especially when interpreting data that reflect a single point in time. Although we adjusted for several covariates, residual confounding may affect study results. A strength of our study is that we were able to assess the roles of multiple ancestries in a single group living in one geographic region, reducing the impact of non-genetic factors that may influence bone density and body composition related to adiposity. These include not only environmental factors such as diet, latitude (and its implications for sunlight) and physical activity, but also non-biological factors such as socioeconomic status that may influence diet quality. Body composition measures were also ascertained using DXA scans, which are highly reproducible measures of body composition. Consistent results across bone sites, particularly for African American ancestry, strengthen the level of evidence for our findings. It is important to note that our findings are based on broad ancestral groups, and assessment of disease risk must still be conducted at the individual level. For example, better understanding of the role of individual genotypes within ancestry may provide a more accurate prediction of risk.

This study contributes to our understanding of complex diseases and disparities in this population and has important implications for other ethnic minorities, particularly those with multiple ancestries. In addition, evaluation of environmental (including diet), cultural and socioeconomic factors that contribute to body composition and related health conditions is essential. Finally, a focus on relationships between genetic and environmental factors, specifically interactions between admixture and environmental factors, may hold promise for individualized approaches in assessing and preventing body-composition-related disease.

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Table 1

Characteristics for 652 participants from the Boston Puerto Rican Osteoporosis Study (BPROS)

Characteristics	Males (*n* = 184)	Females (*n* = 468)	*P* value
Age, years	60.2 ± 7.7	60.6 ± 7.3	0.57
Education			
<5th grade	17 %	25 %	0.04
5–8th grade	27 %	26 %	
9–12th grade (or GED)	43 %	33 %	
Some college or higher	13 %	15 %	
Ancestry			
European admixture	0.56 ± 0.16	0.57 ± 0.15	0.55
African admixture	0.28 ± 0.16	0.28 ± 0.15	0.98
Native American admixture	0.16 ± 0.07	0.15 ± 0.06	0.14
Bone mineral density, g/cm^2			
Total body	1.27 ± 0.12	1.16 ± 0.11	<0.001
Trochanter	0.98 ± 0.11	0.91 ± 0.09	<0.001
Femoral neck	1.07 ± 0.17	1.00 ± 0.15	<0.001
Total hip	1.18 ± 0.14	1.10 ± 0.12	<0.001
Lumbar spine (L2–L4)	1.23 ± 0.21	1.13 ± 0.18	<0.001
Percent fat mass, %	29 ± 8.0	45 ± 6.0	<0.001
Percent lean body mass, %	67 ± 7.0	52 ± 6.0	<0.001
Body mass index, kg/m^2	30.0 ± 5.3	33.1 ± 6.7	<0.001
Height, m	1.7 ± 0.06	1.5 ± 0.06	<0.001
Waist circumference, cm	104 ± 14.3	103 ± 14.5	0.78
Physical activity score	32.4 ± 5.6	31.0 ± 4.0	<0.001
Dietary vitamin D, IU	5.02 ± 3.0	4.73 ± 3.1	0.28
Dietary calcium, mg	880 ± 433	783 ± 413	0.009
Vitamin D supplement use, %	15 %	31 %	<0.001

Table 2

Associations of genetic ancestry with bone mineral density (BMD) at the total hip, trochanter, femoral neck and lumbar spine (L2–L4) regions

	European admixture			African admixture			Native American admixture		
	β	**SE**	***P* value**	***β***	**SE**	***P* value**	***β***	**SE**	***P* value**
BMD, g/cm^2									
Total hip									
Model 1	−0.069	0.04	0.082	0.079	0.039	0.043	−0.07	0.099	0.458
Model 2	−0.056	0.037	0.135	0.062	0.037	0.09	−0.048	0.088	0.587
Trochanter									
Model 1	−0.053	0.024	0.024	0.072	0.023	0.002	−0.122	0.056	0.03
Model 2	−0.047	0.023	0.039	0.064	0.022	0.004	−0.11	0.054	0.04
Femoral neck									
Model 1	−0.101	0.037	0.007	0.123	0.036	0.001	−0.146	0.088	0.099
Model 2	−0.095	0.037	0.010	0.115	0.036	0.001	−0.135	0.087	0.122
Lumbar spine (L2–L4)									
Model 1	−0.035	0.049	0.477	0.071	0.048	0.136	−0.218	0.115	0.058
Model 2	−0.026	0.048	0.584	0.061	0.047	0.200	−0.202	0.113	0.074

Model 1 is adjusted for age and sex

Model 2 is adjusted for model 1 plus BMI

Adjustment for height attenuated associations between admixture and BMD with the exception of African admixture and BMD of the femoral neck [$\beta = 0.78$ (SE 0.35), $P = 0.027$]

Table 3

Associations of genetic ancestry with percent fat mass, percent lean body mass and waist circumference

	European admixture			African admixture			Native American admixture		
	β	**SE**	***P* value**	***β***	**SE**	***P* value**	***β***	**SE**	***P* value**
Fat mass, %									
Model 1	−0.02	0.02	0.26	0.02	0.02	0.35	0.02	0.04	0.71
Model 2	−0.02	0.02	0.23	0.02	0.02	0.29	0.01	0.04	0.78
Lean mass, %									
Model 1	0.02	0.02	0.25	−0.02	0.02	0.33	−0.02	0.04	0.70
Model 2	0.02	0.02	0.22	−0.02	0.02	0.29	−0.01	0.04	0.75
Waist circumference[a], cm									
Model 1	−2.34	3.76	0.53	4.14	3.68	0.26	−10.9	8.87	0.22
Model 2	0.34	2.21	0.87	0.77	2.07	0.71	−6.33	4.99	0.21

Model 1 was adjusted for age and sex

Model 2 was adjusted for model 1 plus education and for height

[a]For waist circumference only, model 2 was adjusted for education and BMI