Ethnic Differences in Bone Mass—Clinical Implications

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Context: Differences in bone mineral density (BMD) as assessed with dual-energy x-ray absorptiometry are observed between geographic and ethnic groups, with important implications in clinical practice.

Evidence Acquisition: PubMed was employed to identify relevant studies. A review of the literature was conducted, and data were summarized and integrated.

Evidence Synthesis: The available data highlight the complex ethnic variations in BMD, which only partially account for observed variations in fracture rates. Factors contributing to ethnic differences include genetics, skeletal size, body size and composition, lifestyle, and social determinants. Despite BMD differences, the gradient of risk for fracture from BMD and other clinical risk factors appears to be similar across ethnic groups. Furthermore, BMD variation is greater within an ethnic population than between ethnic populations. New imaging technologies have identified ethnic differences in bone geometry, volumetric density, microarchitecture, and estimated bone strength that may contribute to a better understanding of ethnic differences in fracture risk.

Conclusions: Factors associated with ethnicity affect BMD and fracture risk through direct and indirect mechanisms. (J Clin Endocrinol Metab 97: 4329–4340, 2012)

Osteoporosis is a global problem characterized by reduced bone strength and increased fracture risk (1, 2). Fifty-six million people worldwide were estimated to have suffered a prior osteoporotic fracture in 2000 (3). Although osteoporosis occurs in all populations, not all populations are at equal risk, as highlighted in a Clinical Symposium at the annual meeting of The Endocrine Society in 2012 (4). The burden of osteoporosis is projected to rise markedly over the next few decades (5), with the greatest increase among elderly non-Whites (6). This review summarizes some of the differences in bone mineral density (BMD) that have been observed between geographic and ethnic groups, and this may contribute to observed fracture rates.

Variation in Fracture Rates

A systematic review identified greater than 10-fold variation in age-standardized hip fracture risk among 63 countries (7). Differences between countries were much greater than the male-female differences within a country. In broad terms, a band of high-risk countries stretched from Northern Europe through middle Europe and then south-eastward to eastern Europe and beyond. Ecological studies have noted a relationship between 10-yr hip fracture probability and latitude (−0.6% increase for each 10° increase in latitude) and also with economic prosperity (1.3% increase for each U.S. $10,000 in per capita gross domestic product) (8). Some have suggested that there may be much greater global variation in hip fracture rates than clinical vertebral fracture rates, although this requires further confirmation given the challenge of accurately measuring vertebral fracture rates (9).

Historical patterns in hip fractures are changing. Hip fracture rates are declining in Western countries but increasing in many developing countries (10), with similar trends for other fracture sites (11–15). Increasing urbanization in developing countries such as China may con-
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Challenges in Studying Ethnicity

Many challenges are encountered in studying ethnic variation in BMD. A systematic review found inconsistent terminology (19). Definitions of ethnicity varied from skin color to language, political group, religion, ancestral group, continental origin or place of birth. Many articles attributed differences to genetic causes, although few actually examined genetic data. Ethnicity, culture, and socioeconomic status are often highly interrelated, which can make associations with BMD difficult to interpret.

Relatively few population-based multiethnic studies have been performed, with most from the United States. Even fewer have prospectively tracked fractures and other explanatory variables that may mediate the effect of ethnicity. Accurate BMD data require rigorous attention to quality control and instrument cross-calibration because calibration differences can be similar to reported ethnic differences. Comparisons between published studies or with manufacturer reference data are therefore problematic.

Recent secular changes in BMD highlight the importance of using contemporary populations. NHANES reported a 6% increase in adjusted femoral neck BMD for non-Hispanic White women in the United States between 1988–1994 and 2005–2008 (20). No consistent change was seen for men or other ethnicities. The Study of Osteoporotic Fractures reported a similar increasing trend for femoral neck BMD between 1992–1997 and 2002–2007 among White women in the United States aged 65 yr and older (21). Factors contributing to increasing BMD and declining fracture rates are not well understood. Obesity is associated with higher BMD and lower hip fracture risk, but it does not account for observed changes (22). Smoking, bone-active medications, overall health status, and calcium and caffeine intake have changed in a favorable direction but have not emerged as the primary explanation (20). The rapidity of these trends has been interpreted as evidence for the predominance of environmental over genetic factors (7).

Ethnic Differences in BMD

In clinical practice, BMD is usually measured with dual-energy x-ray absorptiometry (DXA). In the absence of a fragility fracture, the diagnosis of osteoporosis is based on a T-score of −2.5 SD or lower (23). The World Health Organization (WHO) has suggested that the reference standard for diagnosis of osteoporosis in both genders and all ethnic groups be the femoral neck measured with DXA, where T-scores are derived from the U.S. National Health and Nutrition Examination Survey (NHANES) III database of White women aged 20–29 yr (24–26). There is uncertainty over the applicability of this reference population outside the United States and to non-Whites (27). In clinical practice, other measurement sites such as the lumbar spine, distal radius, and total hip are often used.

DXA has many favorable characteristics, including wide availability, good precision, low radiation dose, and robust ability to predict fractures (28). Overall fracture risk increases approximately 1.5-fold for every SD reduction in BMD and 2.6-fold for hip fracture prediction from hip measurements (29, 30). Most clinical trials have used DXA for enrollment, and DXA plays a pivotal role in most clinical practice guidelines. Notwithstanding these strengths, DXA only evaluates bone mass and does not directly assess bone geometry (bone size, shape, and distribution of material), quality (microarchitecture or turnover), or composition (cortical, trabecular, or transitional zone). DXA calculates BMD (grams per square centimeter) as bone mineral content (BMC; in grams) divided by the projected bone area (square centimeters). As a two-dimensional projectional (areal) technique, DXA does not fully account for skeletal size because it cannot compensate for differences in the unmeasured third dimension (depth). Thus, a larger bone will tend to have higher BMD than will a smaller bone, and comparison of BMD between individuals with different bone sizes can be misleading (31). Indices that attempt to adjust for bone volume (bone mineral apparent density) have been used in research but have not been adopted into clinical practice (31, 32).

A WHO Scientific Group Technical Report noted highly significant differences in BMD in different regions of the world that varied by approximately 1 SD value (33). Variation in BMD between populations is substantially
less, therefore, than the variation in fracture risk noted earlier. Certain ethnic patterns in BMD can be inferred from NHANES: non-Hispanic Blacks have greater femoral neck and lumbar spine BMD than Mexican-American or non-Hispanic Whites across the age spectrum (20, 24, 34). The 95% confidence intervals for mean femoral neck BMD in non-Hispanic Blacks do not overlap the confidence intervals for Mexican-Americans or non-Hispanic Whites (Fig. 1) (20, 35). However, the 95% confidence interval (±2 sd) for non-Hispanic Whites completely encloses the means for non-Hispanic Blacks and Mexican-Americans. The implication is that within-group BMD variation is much larger than between-group variation.

Although NHANES did not report U.S. Asians, a study of 359 adult Chinese-American women found significantly lower BMD at the lumbar spine, total hip, and femoral neck compared with White women (36). Older age at immigration impacted negatively on BMD among postmenopausal women (37). Other studies find substantial ethnic differences in BMD even within those of African or Asian origin (38). African-Caribbean women have the highest mean BMD reported to date for women (39); among South African Black women, hip BMD was greater than White women, whereas total body BMD was similar, and weight-adjusted lumbar spine BMD was lower (40).

### Ethnic Differences in the BMD-Fracture Relationship

The largest multiethnic study to date is the National Osteoporosis Risk Assessment (NORA) Cohort with 197,848 women undergoing a variety of peripheral BMD measurements (41). BMD showed similar fracture discrimination from area under the receiver operating characteristic (AUROC) curve for each ethnic subgroup. BMD predicted 1-yr fracture rates equally well in each ethnic subgroup (1.54-fold for each sd decrease). When ethnicities were compared, some interesting patterns emerged (Fig. 2). Black women had a lower risk for T-score in the osteoporotic range and a similarly lower risk for fracture, whereas Hispanic and Native American women had risks that were not appreciably different from White women. Among Asian women, however, the unadjusted risk for osteoporosis was higher than in White women and was similar after multivariate adjustment (including weight), whereas fracture risk was considerably lower. The Study of Osteoporotic Fractures found that higher BMD among Black women did not fully account for lower fracture rates, with an absolute incidence of fracture 30–40% lower among Black women at every BMD tertile (42). These data suggest very different BMD-fracture relationships in U.S. Black and Asian women.

![FIG. 1. Ethnic variation in femoral neck BMD for females and males. Upper panels show means with ethnicity-specific 95% confidence intervals (CI). Lower panels show means ± 2 sd around the White mean. Data are from 2005–2008 U.S. NHANES (20, 35).](https://academic.oup.com/jcem/article-abstract/97/12/4329/2536344/4331)
Variation among European populations is also present (7). The European Vertebral Osteoporosis Study (EVOS) examined 13 European populations and found a 3-fold range in vertebral deformities and also a highly significant variation in mean BMD (43, 44). However, no significant between-center differences were observed in vertebral deformities after adjustment for BMD, age, body mass index (BMI), and DXA calibration. This was interpreted as showing that differences in BMD explained much of the apparent difference in vertebral fracture risk across sexes and geographical centers in Europe, implying a similar BMD-strength relationship in European populations.

Genetic Factors in BMD

Genetic variation is a potential explanation for ethnic variation in BMD, although conventional ethnicity classifications account for only 5–10% of human genetic variation—indeed, like BMD, most human genetic variation occurs within rather than between ethnic groups (45). Disease susceptibility single-nucleotide polymorphisms (SNPs) exhibit disparity in ancestral allele frequencies across worldwide populations (46). BMD is highly heritable, as is BMD loss, fractures (47, 48), and other determinants of skeletal health including vitamin D metabolism (49), BMI (50), height (51), and possibly even falls risk (52). A recent genome-wide association study evaluated BMD results in 32,961 individuals (replication in 50,933) and fractures in 31,016 cases (over one million controls) (53). Fifty-six SNPs showed genome-wide significance for BMD, and 14 of these loci were associated with fracture risk. No major differences were seen in European subjects vs. over 5200 East Asian subjects, although larger numbers of non-European subjects of greater ethnic diversity are needed to exclude gene-ethnicity interactions. Only 5.8% of femoral neck BMD variation could be explained from 63 SNPs. The AUROC for prediction of osteoporosis was only 0.59 (using 16 BMD-associated SNPs) and only 0.57 for fracture prediction (using 63 BMD-associated SNPs). Adding the SNP score to age and weight alone had a negligible effect on osteoporosis prediction (AUROC, 0.75 vs. 0.76). Thus, the high heritability of BMD appears to be dependent upon a large number of allelic variants with individually very small effect. Although rare variants with large BMD effect may exist, it currently seems unlikely that these will be a primary explanation of ethnic differences in BMD (47). Even if most genes responsible for BMD heritability remain elusive, data from the Women’s Health Initiative provide compelling evidence that genetics affects BMD in U.S. Blacks (54). Women with higher African genetic admixture showed greater BMD than non-Hispanic White women, but also greater rates of bone loss. The authors concluded that genetics may contribute more to peak bone mass, whereas environmental factors may play a major role in age-related bone loss.

Notwithstanding the difficulty in identifying strong susceptibility SNPs for osteoporosis, lessons can be drawn from a comprehensive review of 5065 human genetic studies (46). Type 2 diabetes (T2D) demonstrated extreme directional differentiation of risk allele frequencies, with most T2D risk alleles showing a pattern of decreasing frequencies along human migration into East Asia, which in turn correlated with disparities in genetic risk: T2D was consistently higher for individuals in the African populations and lower in the Asian populations. Thus, differential frequencies of T2D risk alleles contribute to observed ethnic disparities in T2D incidence rates, with ethnicity serving as a proxy for these disease susceptibility genes.

Anthropometry and BMD

Anthropometry contributes to the observed differences in BMD and fracture risk. Greater height, weight, BMI, and lean mass are consistently associated with higher BMD. In ethnically diverse populations, differences in these parameters may explain (or in some cases confound) the relationship between BMD and fracture risk. As noted above, DXA measures areal BMD and cannot fully account for differences in skeletal volume, potentially altering the relationship between measured BMD and fracture risk. In a population of 16,205 White women age 50 yr and older, projected total hip area (in quartiles) was strongly related to likelihood of osteoporosis diagnosis (based upon a T-score of −2.5 or lower), ranging from 14.4% in the smallest quartile to 8.9% for the largest quartile (P < 0.001 for trend) (55). Paradoxically, prior major osteoporotic frac-
tures were less common in those with smaller compared with larger hip area (P < 0.001 for trend). Fewer incident fractures were seen in the smallest vs. largest quartile (major osteoporotic fracture hazard ratio, 0.80; hip hazard ratio, 0.63), in part because larger hip area is a marker for older age due to age-related periosteal skeletal enlargement. Overall, total hip areal BMD categorized more women with smaller bone area as being osteoporotic despite their being younger and at lower fracture risk. Similar findings were reported in 1081 postmenopausal Chinese women (56); there were significant positive correlations between spine bone area and both BMC and areal BMD, but not volumetric BMD. Substantial differences were found in the detection rates of osteoporosis by areal BMD (but not for volumetric BMD) among large (31.4%), intermediate (43.3%), and small-bone area groups (61.7%; P < 0.001).

In 763 Chinese and 424 U.S. White women and men age 40 yr and older, Zhang et al. (57) found significantly smaller bone size (lumbar spine, total hip, femoral neck, trochanter, and intertrochanter) among Chinese subjects. Height was strongly associated with bone size in both ethnic groups and largely explained ethnic and gender differences in bone size. In another comparison with Chinese subjects, White females had 9.3% higher BMD at the spine and 5.8% higher BMD at the hip, whereas femoral neck BMD in White males was 6.2% higher (58). After adjustment for age, height, and weight, ethnicity accounted for less than 3% of BMD variation. A review by Wang et al. (59) concluded that most deficits in areal BMD in Chinese relative to Whites are explained by differences in bone area. However, these historical patterns appear to be changing due to recent secular increases in height and weight—almost 5 cm average increase in height for young Chinese during the last two generations (60–62). How this will affect peak bone mass accrual in China and other countries rapidly undergoing economic development and improving standards of living remains uncertain.

The multiethnic Study of Women's Health Across the Nation (SWAN) examined White, Black, Japanese, and Chinese women living in the United States (mean age, 46 yr) (63). Black women had the highest, whereas Japanese and Chinese women had the lowest unadjusted BMD. BMD correlated positively with weight in all subgroups. Among women of comparable weights, there were no differences in adjusted lumbar spine BMD between Black, Chinese, and Japanese women, all of whom had higher BMD than White women. Similar relationships have been seen in men, where adjustment for weight and height greatly attenuated or even reversed the differences between U.S. White men vs. U.S. Asian, Hong Kong Chinese, and South Korean men (38). The importance of body size has also been demonstrated in non-U.S. populations where ethnic differences in BMD disappeared after adjustment for weight and/or height (64, 65).

The complexity of anthropometric relationships is underscored in Native Canadians, a population with fracture rates two or three times higher than the general population (66). A comparison of BMD at five measurement sites in age-matched White and Native Canadian women found no differences in unadjusted BMD. However, after adjustment for weight or BMI, BMD was significantly lower in Native Canadian women at three of the five measurement sites (67). Simple adjustments based upon weight or BMI may not reflect body composition, and lean mass shows a much stronger effect on BMD than fat mass (67, 68). When lean and fat mass were used in the analyses, no significant differences between White and Native Canadian women were seen for any measurement site. Therefore, weight can give misleading results when groups differ in body composition. U.S. Black women have greater muscle mass and less fat mass as a percentage of body weight than White women, which may account for the different slope of spine BMD vs. BMI (69). The Boston Area Community Health/Bone (BACH/Bone) Survey found that 20–83% of the Black vs. White difference in BMD and BMC was accounted for by body composition (in addition to diet and sociodemographic factors) (68, 70).

**Ethnic Differences in Calciotropic and Gonadal Hormones**

Ethnic differences in calciotropic hormones and calcium conservation were reviewed by Walker et al. (71). Worsening vitamin D status was noted between 1988–1994 and 2001–2004 in all U.S. ethnicities, with vitamin D deficiency (serum 25-hydroxyvitamin D < 10 ng/ml) most common in non-Hispanic Blacks (29% in 2001–2004 vs. 6% overall) (72). U.S. Blacks have lower average calcium intakes, higher serum PTH and calcitriol, and relative PTH resistance from infusion studies (71). Interestingly, there is better daytime urinary conservation of calcium in U.S. Blacks and more efficient intestinal calcium absorption. There has been some suggestion of a different relationship between Blacks and Whites in their response to vitamin D (73), but this remains controversial because other data show a similar positive relationship between BMD and vitamin D status (74). Whether similar patterns exist in African Blacks or other groups is unknown.

Premature ovarian failure differed in the SWAN Study; it was highest in Hispanic and Black women and lowest in Japanese and Chinese women (75). This may in part reflect social factors because premature ovarian failure was as-
sociated with difficulty paying for basics, lower educational level attained, single marital status, and current smoking. Many differences in gonadal hormones among U.S. White, Black, and Asian men have also been noted (76). Asian men in Hong Kong and Japan, but not in the United States, had higher levels of total testosterone than other groups, suggesting that geographic factors may be as important—if not more important—than ethnicity.

### Lifestyle and Social Factors

Lifestyle factors differ according to ethnicity, including sunlight exposure, smoking, exercise, alcohol consumption, and dietary calcium intake. However, there is little evidence that these risk factors behave differently in one population than another. The WHO Fracture Risk Assessment (FRAX) tool integrates multiple clinical risk factors including (optionally) femoral neck BMD to determine a 10-yr absolute fracture probability for major osteoporotic fractures and hip fractures (33). The FRAX algorithm assumes that the relative risk of BMD and other risk factors is the same across populations. Meta-analyses conducted by the WHO tested for heterogeneity between populations from Europe, North America, Australia, and Japan. Seven of the eight risk factors did not show a significant interaction (the exception was prior fragility fracture, which may be related to question construct) (33). Among Native Canadians, the relative risk for diabetes, alcohol/substance abuse, or multiple comorbidities was the same as in the general population (77). However, because the prevalence of these risk factors was much greater in Native Canadians, they imparted a significantly greater population-attributable risk.

Risk factors for fracture are more commonly observed in those of greater social disadvantage, including nutritional inadequacies, smoking, physical inactivity, and comorbidities (78). A systematic review found a positive association between BMD and educational attainment in women (79). A subsequent report identified BMD associations with income and/or education among postmenopausal women and men from a broad range of populations (U.S. White, U.S. Black, China, Turkey, Italy, and Korea) (80). The strongest correlates of BMD in South African Black vs. White young women were for lifestyle (walking for travel vs. leisure activity) and social factors (injectable vs. oral contraception), in addition to body composition (fat and fat-free soft tissue mass) (40). Low family poverty-to-income ratio was associated with higher bone turnover in U.S. men, whereas Black women had higher bone turnover, attributed by the authors to “higher levels of social stress” (81). Height, which correlates with skeletal size, is a general indicator of health, income, and socioeconomic status (82). A systematic review noted that in low- to middle-income countries, large height differences are seen across income and educational levels, with a positive association between wealth and height demonstrated in 52 of 54 countries (82). In summary, low socioeconomic status may affect fracture risk through BMD-dependent and BMD-independent mechanisms.

### Ethnic Differences in Osteoporosis Care

Fracture rates are lower in U.S. Blacks and Asians, but the burden of osteoporotic fractures is still substantial across all ethnicities (83, 84). Ethnic disparities in osteoporosis screening, prevention, and treatment have been noted even among individuals at similarly high risk (85, 86). Neuner et al. (87) examined Medicare records for 35,681 females with hip fractures. Black women were half as likely and Hispanic women were two thirds as likely as White women to undergo BMD testing before fracture, and they remained much less likely to undergo BMD testing after fracture. Even in a national healthcare system where individuals do not pay for BMD testing, large socioeconomic discrepancies have been reported (88). After a major osteoporotic fracture, Native Canadians were one half to one tenth as likely to receive BMD testing, osteoporosis treatment, or an osteoporosis diagnosis than the general population (89).

Ethnic differences impact on treatment eligibility under the National Osteoporosis Foundation Guidelines (90). Using NHANES 2005–2008 data for those aged 50 yr and older, the prevalence of osteoporosis of the femoral neck ranged from 6.0% in non-Hispanic Black women to 12.6% in Mexican-American women. Spinal osteoporosis was more prevalent among Mexican-American women (24.4%) than among either non-Hispanic Blacks (5.3%) or non-Hispanic Whites (10.9%). Treatment eligibility was similar in Mexican-American and non-Hispanic White women (32.0 and 32.8%) and much higher than in non-Hispanic Black women (11.0%). Treatment eligibility among men was 21.1% in non-Hispanic Whites, 12.6% in Mexican-Americans, and 3.0% in non-Hispanic Blacks.

### Advanced Imaging Techniques

Although BMD assessed with DXA predicts 60–80% of bone strength (91), there is still considerable overlap in measurements between fracture and nonfracture subjects (92–94). Simple DXA-derived geometric parameters can be used to estimate strength indices using the hip structure...
analysis technique of Beck et al. (95). In a subset of the SWAN cohort, 1940 perimenopausal and early menopausal women underwent determination of bone strength parameters (96). Compressive, bending, and impact strength indices were all significantly better in African, Chinese, and Japanese-American women compared with White women, consistent with their lower fracture rates. Hip axis length is measured on DXA as the distance from the base of the greater trochanter to the inner pelvic brim and is positively associated with height and hip fracture risk (97, 98). Compared with Whites, some studies have reported hip axis length to be lower in those of African or Asian origin (99–101), whereas others have not found consistent ethnic differences (102–104).

More detailed assessments of bone geometry and microarchitecture are provided by cross-sectional imaging modalities (105). High-resolution peripheral quantitative computed tomography (HR-pQCT) was used to examine the distal radius and tibia in 173 White and 100 Black women from the SWAN cohort. Black women had greater bone area, cortical area, cortical bone volume, and trabecular thickness, which would all contribute to the higher bone strength. HR-pQCT has also been used to assess skeletal differences between premenopausal Chinese and White women (106, 107). This confirmed reduced bone size among Chinese women, but also identified higher cortical and trabecular thickness resulting in higher volumetric BMD. Postmenopausal Chinese women had smaller bone size with greater cortical thickness and cortical BMD. More favorable trabecular structure (plates vs. rod-like junctions) were also seen among the Chinese women (108). These differences may contribute to the lower fracture rates in Chinese vs. White women, particularly when considering that lower body weight and shorter height among Chinese women would exert lower stress on bone during falling. Further support for this thesis comes from the multiethnic SWAN study; composite measures, which integrate indices of skeletal strength (using femoral neck BMD) and skeletal loading (using weight and height), were unaffected by ethnicity information ($P = 0.11–0.22$), whereas ethnicity modified fracture risk independent of BMD ($P = 0.02$) (109). Thus, a better understanding of skeletal biomechanics may eliminate the need to consider ethnicity as a primary risk factor, but this needs to be confirmed in studies from other parts of the world.

**Implications for Fracture Risk Assessment**

Current DXA software provides a very limited range of ethnicity choices, but importantly, this does not affect the T-score calculation, which is based upon White reference data as recommended by the International Society for Clinical Densitometry (ISCD) (27). Ethnicity affects the Z-score (already sex and age-matched) because the Z-score is intended to compare measured with expected BMD in an individual, and it is not used for fracture risk assessment.

Although BMD is an important correlate of fracture risk, the majority of fragility fractures occur in individuals with measurements above the osteoporotic range (92–94). The WHO FRAX tool provides a more complete assessment of fracture risk by considering additional BMD-independent clinical risk factors (33). The FRAX tool is calibrated to a specific country and population based upon fracture and mortality rates. With identical inputs (including femoral neck BMD), the output from FRAX is highly dependent upon the specific calculator (7). The country with the highest major fracture probabilities (Denmark, 23% for men and 27% for women at a T-score of $-2.5$) is several fold higher than the country with the lowest fracture probabilities (Tunisia, 1.9% for men and 2.4% for women). There are also large differences in FRAX probabilities between U.S. ethnicity-specific calculators. Figure 3 shows that for hypothetical women age 50 with BMI of 25 kg/m² and prior fragility fracture, using femoral neck BMD that is average for ethnicity or average for White females minimally alters the FRAX output (96). Specifically, the output from the U.S. Black calculator is less than half the output from the U.S. White calculator, with the U.S. Asian calculator giving intermediate results. The FRAX calculator for China (Hong Kong) gives considerably lower fracture probability than the U.S. Asian calculator (and even lower than the U.S. Black calculator), whereas the FRAX calculator for Japan gives a significantly higher prediction (although still less than for U.S. White). Thus, fracture risk relationships are complex within and between populations, even when there is

![FIG. 3. Effect of ethnic differences in BMD on major osteoporotic fracture probability in a woman age 50 yr with a prior fracture (FRAX version 3.6). BMD data are from the Study of Women Across the Nation (SWAN) (96).](https://academic.oup.com/jcem/article-abstract/97/12/4329/2536344/3)
shared ancestry. The current version of FRAX (version 3.6) offers 50 calculators, and therefore only a minority of countries and a fraction of the world’s ethnicities are represented. Most countries without a FRAX calculator have little or no good-quality fracture data, a situation addressed in joint positions from the ISCD and International Osteoporosis Foundation (110). Using a FRAX calculator from the same region for a country with similar lifestyle, socioeconomic conditions, and life expectancy can be considered. As a general rule, the larger the population available for calibrating a risk calculator, the more accurate the predictions. Therefore, when there is no validated ethnic calculator, or where ethnicity is unknown or mixed, using the calculator for the numerically predominant ethnicity is reasonable (e.g. U.S. White FRAX calculator for Native Americans) (110).

Two different approaches to ethnicity are evident among the currently available FRAX tools. Two countries have ethnicity-specific calculators: the United States (White, Black, Asian, and Hispanic) and Singapore (Chinese, Malay, Indian). All other countries, many with equally complex ethnic structures, have adopted a single calculator. The argument for multiple ethnic calculators derives from differences in fracture rates and mortality as outlined above. However, this assumes that a single calculator can be applied to the wide diversity that exists within (not just between) ethnic groups that share the same continental origin. A country’s ethnic traditions and political needs and the availability of adequate ethnic fracture data must all be considered in choosing between one vs. multiple ethnic risk calculators. As noted earlier, there is variation among European subgroups (43, 44) and in relation to African admixture (54). The U.S. FRAX Hispanic and Asian calculators may underestimate risk within subgroups of Hispanics and Asians (110); therefore when fracture risk is estimated with these tools, clinical judgment is still required to interpret what this means for the individual and the likelihood of benefit from treatment.

**Summary**

There are complex interrelationships between ethnicity, BMD, and fracture risk (Table 1). Just as multiple mechanisms contribute to fracture risk independent of BMD, ethnicity is much more than genetic ancestry, affecting osteoporosis and fractures through biological pathways and behavioral and social factors that impinge on determinants of bone strength and falls risk (Fig. 4). Genetic ancestry, anthropometry, lifestyle, comorbidities, and social factors all contribute to fracture risk through BMD-dependent and BMD-independent mechanisms. The relative proportions of these are likely to differ between ethnic groups; the case for genetic ancestry is strongest for U.S. Blacks, and the effect of skeletal size is strongest for Asians.

**TABLE 1. Factors that contribute to ethnic differences in BMD and fracture risk**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example</th>
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<tbody>
<tr>
<td>Genetics</td>
<td>Higher BMD and lower fracture risk in Americans with greater African genetic admixture (54)</td>
</tr>
<tr>
<td>Skeletal size</td>
<td>Lower areal BMD in Chinese largely due to smaller bone size (59)</td>
</tr>
<tr>
<td>Weight</td>
<td>No differences in spine BMD for Black, Chinese, and Japanese women of comparable weight, but all higher than White women (63)</td>
</tr>
<tr>
<td>Body composition</td>
<td>Weight-adjusted lower BMD in Native Canadian women disappeared when adjusted for lean and fat mass (67)</td>
</tr>
<tr>
<td>Calcitropic hormones</td>
<td>High prevalence of vitamin D insufficiency in non-Hispanic Blacks (72) with higher serum PTH and serum calcitriol suggesting relative PTH resistance (71)</td>
</tr>
<tr>
<td>Gonadal hormones</td>
<td>Premature ovarian failure more common in Hispanic and Black women and lowest in Japanese and Chinese women (75)</td>
</tr>
<tr>
<td>Social position</td>
<td>Lower BMD, higher fracture rates but lower rates of BMD screening</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>Lower rates of osteoporosis screening, prevention, and treatment among Black women (85, 86)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>Black women and Hispanic women less likely to undergo BMD testing after fracture (87)</td>
</tr>
<tr>
<td>Skeletal geometry and microarchitecture</td>
<td>HR-pQCT shows higher cortical and trabecular thickness (resulting in higher volumetric BMD) (106, 107) and more favorable trabecular structure in Chinese vs. White women (108)</td>
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**FIG. 4.** A conceptual framework for mechanisms through which ethnicity may affect BMD and fracture risk. [Modified from W. D. Leslie and B. Lentle: Race/ethnicity and fracture risk assessment: an issue that is more than skin deep. J Clin Densitom 9:406–412, 2006 (111), with permission. © Elsevier.]
Historical patterns of BMD and fracture may be changing with the recent increase in BMD among White women in the United States and increasing height among Asians. Generalizations should not become stereotypes because it is the individual’s risk factor profile that is most important in determining his/her fracture risk. Prevention efforts should target multiple risk factors of all individuals, regardless of ethnicity. For example, smaller skeletal size applies to many, but certainly not all Asians, whereas higher BMD may characterize the “average” U.S. Black, but osteoporosis still occurs among a substantial minority of Black men and women. BMD variation, like genetic variation, is greater within an ethnic population than between ethnic populations. Evidence to date suggests that the relative risk of BMD and other clinical risk factors on individual fracture risk is similar across populations. Advanced imaging techniques may lead to better understanding of human diversity in BMD, skeletal strength, and fracture risk.

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