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Relative Contributions of Multiple Determinants to Bone Mineral Density in Men

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Abstract

Introduction—Osteoporosis in men has gained recognition as a public health problem, generating an interest in the search for risk factors. Isolation of individual risk factors could allocate disproportionate attention to relationships that may be of limited consequence.

Methods—The Boston Area Community Health/Bone (BACH/Bone) Survey is a population-based study of randomly-selected community-dwelling men (age 30–79 y). Bone mineral density (BMD) and lean mass were measured by dual x-ray absorptiometry. Socioeconomic status, health history, and lifestyle factors were obtained via interview. Hormone levels and markers of bone turnover were obtained from non-fasting blood samples. Multivariate analyses measured relative contributions of covariates to femoral neck (hip), 1/3 distal radius (wrist), and lumbar spine BMD.

Results—Factors positively associated with BMD in multivariate models at the three sites were black race and appendicular lean mass. Asthma was consistently negatively associated. Various other risk factors also contributed significantly to each of the individual sites. R^2 values for the hip, wrist, and spine were 41%, 30%, and 24% respectively. Lean mass accounted for the most explained variance at all three sites.

Conclusions—These data emphasize the limitation of focusing on individual risk factors and highlight the importance of potentially modifiable lean mass in predicting BMD.

Keywords

aging; body composition; bone mineral density; men; population studies

Introduction

Osteoporosis in men has gained wide recognition as an understudied public health problem, generating increased attention to male bone fragility as well as new focus on identification of risk factors and potential avenues of prevention. Numerous risk factors have been identified including but not limited to age,(1,2) hormone concentrations,(3–5) serum measures of bone metabolism,(6–9) lifestyle factors,(10–12) body composition,(13–15) decreased physical activity,(12,16) and medication use.(17,18) Recent publications have highlighted the most important risk factors for osteoporosis, fracture risk, and low bone mineral density (BMD) in men.(19,20)

Research on the potential risk factors for osteoporosis, fracture risk, and low BMD to date has generally focused on one risk factor at a time. As a result, it is possible that disproportionate

attention may be given to factors whose relation to osteoporosis, fracture risk, or BMD is spurious or of limited clinical relevance. This highlights the need for assessment of the *relative* importance of risk factors as contributors to bone fragility. As has been the case with other diseases,(21,22) there has been limited attention given to the relative importance of contributors to bone fragility. Most existing attempts (23-32): 1) are restricted to relatively few potential risk factors, 2) make sample exclusions which eliminate some potential factors, 3) do not include men, 4) are confined to homogeneous populations, and/or 5) are derived from convenience samples.

A recent investigation from The Osteoporotic Fractures in Men Study (MrOS) provided a detailed examination of a large set of potential contributors to decreased BMD in older men. This study showed that body weight, neuromuscular function, personal and family history of fracture, diabetes, race and ethnicity, and the use of selected medications were the factors most strongly correlated with BMD.(33)

In this report, we consider a large class of potential contributors to BMD using data from the cross-sectional Boston Area Community Health / Bone (BACH/Bone) Survey, an observational study of N=1,219 randomly-selected, community-dwelling men between the ages of 30-79 y. Our primary objective is to establish the relative contributions of these factors to inter-subject variation in BMD at three skeletal sites: the hip (femoral neck), wrist (1/3 distal radius), and lumbar spine (L1-4). BMD at these sites has been shown to predict fractures. (34-37)

Materials and Methods

Design

The BACH/Bone Survey is a cross-sectional investigation of bone health among 1,219 community-dwelling black, Hispanic, and white men, specifically designed to test hypotheses about race/ethnic differences in skeletal health. BACH/Bone enrolled subjects from the larger Boston Area Community Health (BACH) Survey, a study of 5,501 randomly selected black, Hispanic, and white male and female Boston, MA residents, ages 30 to 79 years. The BACH Survey employed a multistage stratified cluster design to recruit a random sample, obtaining approximately equally-sized subsamples by gender, race, and age group (30-39 y, 40-49 y, 50-59 y, 60-79 y); baseline data were collected between April 2002 and June 2005.

Following the BACH in-person interviews, male respondents (N=2,301) were invited to participate in an additional study on bone health (the BACH/Bone Survey). Exclusion criteria were weight greater than 300 lbs, inability to lift self onto the scan table, and relocation from study area. Between November 2002 and July 2005, 1,219 (65%) of 1,877 eligible BACH men were enrolled in BACH/Bone; 1,209 of these subjects completed DXA scans.

The parent BACH Survey protocol was approved by the New England Research Institutes (NERI) Institutional Review Board (IRB) and the BACH/Bone protocol was approved by IRBs at both NERI and BUSM. Written informed consent for each study participant was obtained independently. Extensive information concerning the BACH and BACH/Bone designs and sampling procedures has been previously published.(1,38)

Data Collection

Interviews and measurements for BACH and BACH/Bone were conducted by trained staff at NERI and the BUSM's General Clinical Research Center (GCRC), respectively. Data collection for BACH generally occurred in participants' homes. Data used in this investigation from BACH included demographic characteristics (age, education, household income, marital status), health status (including family history and self-report of comorbid conditions such as

asthma and high blood pressure), a comprehensive collection of prescription and over-the-counter medication use, and lifestyle attributes (alcohol use, diet with Block food frequency questionnaire,(39) physical activity using the Physical Activity Scale for the Elderly (PASE), (40) and smoking). Race/ethnicity was determined according to the federal standard.(41) Men who were screened as not of black, Hispanic, or white origin were excluded by design from BACH.

A non-fasting blood sample was collected close to waking time in BACH to control for diurnal variation in hormone levels (42,43) (median time since awakening 3 h 38 min). Serum samples were stored at -80°C until analysis. Testosterone (T), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) were measured at the Children's Hospital Medical Center Research Laboratories (Boston, MA) by competitive electrochemiluminescence immunoassays on the 2010 Elecsys system (Roche Diagnostics, Indianapolis, IN). The lower limits of detection for T, LH, FSH, and SHBG were 2 ng/dL (0.07 nmol/L), 0.10 IU/L, 0.10 mIU/mL, and 3 nmol/L, respectively. The inter-assay coefficients of variation (CV) for T at concentrations of 24-700 ng/dL (0.83-24.31 nmol/L) were 7.4-1.7%, 5.2-2.0% for LH at concentrations of 0.5-50.7 IU/L, 3.8-5.3% for FSH at concentrations between 1.2-103 mIU/mL, and 2.4-2.7% for SHBG at concentrations between 25-95 nmol/L. Estradiol (E2) was measured at the Mayo Clinic Core Laboratory (Rochester, MN) with liquid chromatography-tandem mass spectrometry. The lower limit of detection was 12.5 pg/mL (46 pmol/L). E2 values less than 12.5 pg/mL (46 pmol/L) were calculated by manual integration of chromatograms. The inter-assay CVs for estradiol concentrations 1.25-60 pg/mL (4.6-220 pmol/L) ranged between 13.4-6.0%. Free T and E2 concentrations were calculated from total T or E2 and SHBG concentrations using mass action equations.(44,45)

As part of the BACH/Bone study, BUSM GCRC staff performed the DXA scan, obtained anthropometric data, and other information. Scans of the femoral neck, 1/3 distal radius, and anteroposterior lumbar spine were performed using a Hologic QDR 4500W densitometer (Hologic, Inc., Waltham, MA). DXA scans were performed and analyzed by trained and certified technicians. The DXA system was monitored weekly for drift. CVs were less than 1.5%.(46) Body composition measures, including total body and regional fat mass (FM) and nonfat mass, were also obtained. Lean mass (LM) was calculated by subtracting the bone mineral content from nonfat mass. Appendicular lean mass (ALM) was generated by adding the relevant quantities for subjects' arms and legs.

A non-fasting BACH/Bone blood sample, obtained on average approximately 36 days after BACH, was collected from each subject. This sample was obtained throughout the day (median: 11:25am, min: 7:45am, max: 7:40pm) and was used to measure 25-hydroxyvitamin D [25(OH)D] [25(OH)D₂ + 25(OH)D₃], bio-intact parathyroid hormone (PTH), calcium, and bone turnover markers. The 25(OH)D was measured in duplicate by a competitive protein binding (CPB) assay without prior chromatography as previously described.(47) Inter-assay CVs were less than 15%. The lower limit of detection for the serum 25(OH)D assay was 5 ng/mL (12.5 nmol/L). PTH was measured with the Nichols Advantage System (Nichols Institute Diagnostics, San Clemente, CA) (inter-assay CVs were less than 8.3%), as was calcium (Arsenazo III, Quest Diagnostics, Cambridge, MA). Markers of bone turnover included serum intact osteocalcin (OC), a marker of bone formation, and serum C-terminal telopeptides of Type-1 collagen (CTx), a marker of bone resorption. OC was measured in duplicate with the Nichols Advantage System (Nichols Institute Diagnostics, San Clemente, CA) and CTx was measured with Serum CrossLaps ELISA (Nordic Bioscience Diagnostics, Herlev, Denmark). Inter-assay CVs for OC and CTx were less than 10% and 8.1%, respectively.

The physical function tests in BACH/Bone included a timed walking test (time needed to walk 50 ft) and a chair stand test (time needed to stand up and sit down five times with arms folded).

Following Guralnik et al.(48) we created a composite “physical function” variable as follows: those completing the walking test and chair stands test were assigned scores of 1-4 per test, corresponding to the quartiles of time needed to complete the test, with the fastest time scored 4. Those who could not complete the test were assigned a score of 0. The scores from the walking and chair stands tests were summed together. Since only one subject was not able to complete the walking task, we included that subject with those who were in the longest quartile of walking times. Thus, the score ranges from 0- 7.

Additional data collected for the BACH/Bone Survey included height by stadiometer, weight by digital scale, changes in medication use between BACH and BACH/Bone, vitamin supplement use, and grip strength with a Jamar hydraulic hand dynamometer. Sunlight exposure was assessed with the question, “Over the past 3 months, about how many hours per week did you usually spend outside. Please include daylight hours only,” with possible answers of <1 h, 1 to <2 h, 2 to <4 h, 4 to <7 h, or 7+ h.

Analytic Sample

Of the 1,209 male participants who completed DXA scans, we excluded 20 subjects taking thyroid hormones and 27 subjects taking oral/systemic corticosteroids (as well as budesonide and flunisolide) because both groups of medications have been shown to be related to BMD, and because there were too few subjects to statistically measure any true relationship. Thirty-four subjects missing a DXA scan (either hip, wrist, and/or spine) were also excluded. This left 1,128 men (93%) as a base analysis sample.

Due to missing data for selected covariates, more specific analysis samples were developed for each BMD site. From the base sample of 1,128 men, the final hip BMD sample was reduced to N=686 (28 missing measures of body composition, 3 missing data on asthma status, 160 missing data on caffeine consumption, 3 missing years of education, 2 did not complete the PASE questionnaire, and 246 did not have a free E2 (FE2) value). For the final wrist model, the base sample was reduced to N=985 (28 missing measures of body composition, 3 missing data on asthma status, 2 missing data related to cancer, and 110 missing grip strength measurements). Similarly, the final spine BMD sample contained 873 men (28 missing lean mass measures, 3 missing data on asthma, 160 missing data on caffeine consumption, and 64 were missing a value for CTx).

Statistical Methods

To account for the complex sampling design, the following analyses were conducted using SUDAAN 9.0. First, covariates were tested in age-adjusted linear regression models modeling BMD at the hip, wrist, and spine (see full list of covariates in Table 1). Covariates meeting a minimal criterion for association with outcomes ($p \leq .20$) in these age-adjusted regressions were organized into groups (e.g., “lifestyle”). Smaller multivariate models containing only the variables within a group were tested at all three sites in order to determine which covariates within the group were most strongly associated with the outcomes. Backwards stepwise elimination of non-significant covariates was performed on these models using a stronger criterion for association ($p \leq .10$). Finally, a larger multivariate linear regression model was produced containing all variables remaining from each sub-model. We again employed backwards elimination ($p \leq .10$) in order to reach a more parsimonious “final” model.

We used R^2 to compare the relative contributions of the groups of variables left in the final model. The R^2 for the final model was recorded and each group was removed individually, always controlling for all other variables in the final model. The change in R^2 , denoted by ΔR^2 , was recorded for removal of each group. Each ΔR^2 was then divided by a sum of the ΔR^2 s in order to illustrate the relative contribution of each subgroup:

$$\frac{\Delta R_i^2}{\sum_{i=1}^n (\Delta R_i^2)} \times 100$$

where i = each of the groups and n = number of groups. This method is a generalization of the R^2 method used in previous publications.(49) The result from this equation is a percentage of the contribution of a group of variables to the sum of the differences in R^2 from all variable groupings. For this analysis, we use this percentage to estimate the contribution each group of variables makes to the explained variance. In this final step, age was considered on its own in order to capture age differences not expressed by the other covariates.

All models containing ALM were adjusted for height and all models with markers of skeletal metabolism (i.e., OC, CTx, 25(OH)D, serum calcium, and PTH) were adjusted for time of day and season of measurement. Additional analyses testing for variation in covariates by race/ethnicity were performed using interaction terms in the final models.

Results

Summary statistics for the three samples are displayed in Table 1. There was little variation of characteristics between the samples, with subjects aged approximately 47y and with ALM of about 27kg. Seven percent of subjects were taking selective serotonin reuptake inhibitors (SSRIs) and about 15% of subjects reported a diagnosis of asthma. Additionally, almost half of the subjects were non-smokers and about 15% reported over 20 smoking pack-years.

Variables shaded gray in Table 1 were not significantly associated ($p>.20$) with hip, wrist, or spine BMD in the initial age-adjusted models, and were therefore not considered in future multivariate regression models. For example, free T and the physical strength composite did not contribute to BMD at any of the three sites ($p>.50$), nor did a grouping of drugs known to increase bone metabolism (including calcium supplements, vitamin D supplements, and/or anabolic steroids) ($p>.22$). In an additional analysis (not shown), a count of these drugs categorized into 0, 1, or 2+ showed no significant effect on BMD and no dose-response relationship. No covariates in final models at any site had a significant interaction with race/ethnicity.

Hip BMD

Table 2 displays the age-adjusted linear regressions of the sub-models after backwards stepwise elimination for hip BMD. In these sub-models, age had a large association with hip BMD; with each decade increase, BMD was lower by 0.034 g/cm² ($p<.001$). Similarly, strong associations were observed for race/ethnicity in the demographics sub-model, ALM in the body composition sub-model, FE2 in the hormone sub-model, caffeine intake in the lifestyle sub-model, arthritis in the health sub-model, and grip strength in the function sub-model (all $p<.001$).

The results of the final multivariate model for hip BMD are shown in Table 2. These results show a positive association with ALM and physical activity to BMD, as well as an inverse association of caffeine consumption to BMD. As in the demographics sub-model, black men had a higher average BMD than white and Hispanic men.

The R^2 statistic reveals that the final model accounted for a total of 40.5% of inter-individual variation in hip BMD. Figure 1 illustrates the non-confounded R^2 contribution of each sub-group. Of the contributing groups, the body composition group was the most powerful

explanatory factor with height-adjusted ALM contributed nearly 60% of the change in R^2 . The next largest contributor (17%) was demographics (education, race/ethnicity). Age itself contributed 7% of the change in R^2 , and all other groups contributed less than 5% each.

Wrist BMD

Table 3 displays the results for wrist BMD models. The center column illustrates the outcomes from age-adjusted linear regressions of the sub-models after backwards stepwise elimination. Similar to results in the hip BMD model, age, ALM, race/ethnicity, and several other variables were significant predictors of wrist BMD. However, no final hormone variables were associated in the wrist sub-models and many groups (lifestyle, demographics, serum, and function) were reduced to only one significant contributor. SSRIs, arthritis, and diabetes were the strongest contributors to wrist BMD in the health sub-model.

In the final model for wrist BMD (Table 3), there was a strong positive association between wrist BMD and black race, ALM, and grip strength. SSRIs and asthma had significant negative correlations with BMD at the wrist.

The R^2 statistic reveals that the final model for wrist BMD accounted for a total of 30% of inter-individual variation. As with the hip data, the body composition group was the most powerful explanatory factor (see Figure 2), contributing 43%. Function (grip strength) (23%), demographics (race/ethnicity) (21%), and health (asthma, cancer, SSRIs) (12%) were also major contributors. Hormones were not associated in the previous analytical step, and due to non-significance of their components, lifestyle and bone-related serum measures were also eliminated from the final wrist model. Age contributed 0.1% the change in R^2 .

Spine BMD

Table 4 displays the age-adjusted linear regressions of the sub-models after backwards stepwise elimination for spine BMD. Strong associations were observed for race/ethnicity in the demographics sub-model. Other important correlations in the spine sub-models included: ALM in the body composition sub-model, caffeine intake in the lifestyle sub-model, asthma in the health sub-model, grip strength in the function sub-model, and CTx in the serum sub-model (all $p \leq .001$). Chronic lung disease was also a strong predictor of spine BMD.

The final multivariate model for spine BMD is displayed in Table 4. Age, black race, and ALM show strong positive correlations even after adjustment for the other risk factors. Caffeine intake, asthma, chronic lung disease, and CTx all demonstrated negative cross-sectional relationships with spine BMD.

The R^2 statistic revealed that this model explained 23.5% of the variance in spine BMD. Figure 3 illustrates the comparison of the non-confounded R^2 contribution of each sub-group. Of the contributing groups, the body composition group was the most powerful explanatory factor. Body composition (ALM, height) contributed about 43% of the change in R^2 . The other large contributors were demographics (race/ethnicity) with 17%, serum (CTx) with 14%, age with 11%, and health (asthma, chronic lung disease) with 11%. Lifestyle factors (caffeine intake) contributed less than 5% of the change in R^2 .

Discussion

In this population-based study of men aged 30 to 79, we considered the correlation of a wide range of previously identified risk factors for low BMD, osteoporosis, and fracture risk with BMD levels in the hip, wrist, and spine. As hypothesized, BMD is independently associated with a large number of these factors. Adjusting for all strongly related factors, ALM shows the most robust association with BMD at all three sites. Race/ethnicity and health status are also

strong contributors to BMD. Additionally, results of this study show that lifestyle factors are important to BMD in the hip, while grip strength is strongly related to wrist BMD, and age and CTx are important to BMD in the spine.

The results of this study suggest that BMD in the hip, wrist, and spine have some common contributors, with ALM showing the most robust association with BMD at all three sites. Interestingly, ALM has a positive association not only with the weight-bearing hip and spine BMD, but also with BMD in the wrist. This provides evidence to support the notion that muscle forces rather than absolute mass contribute to BMD. These results may have implications for fracture prevention. In addition, there are racial/ethnic differences in BMD common to all sites. As also shown in other studies with diverse samples,(33,50) black men have significantly higher BMD than Hispanic or white men, even in the presence of multivariate adjustment. In unadjusted models, we have previously reported(1) that Hispanic men have higher average BMD than white men; however, this difference becomes negligible at all three sites after adjustment for the factors in this analysis. Finally, asthma has a consistent inverse correlation with BMD. Since subjects currently using strong corticosteroids were removed from the sample, possible explanations for this observation are many and may include residual confounding by physical activity(51) or systemic inflammation,(52) which was not considered in this report.

Our results also show some key differences between the three sites. First, we note that a larger percentage of the variance in hip BMD can be explained than in wrist or in spine BMD (41% (hip) vs. 30% (wrist) and 24% (spine)). One possible reason is the larger number of variables in the hip model compared to the other two models. We re-analyzed the wrist and spine models with all of the factors included in any of the individual site models (hip, wrist, and spine). The wrist model R^2 increases from 30% to 34% and the spine model R^2 increases from 24% to 29%. In spite of these increases, the R^2 values do not reach the percentage of variance explained in the hip model, suggesting that the difference is not entirely a function of the number of factors in the model.

Another difference is the varying effect of age in each model. Results of our analyses show that age has a strong negative association with hip BMD, but has no significant association with wrist BMD. This is consistent with the observation that among men, the incidence of hip fracture increases substantially with age but Colles' fracture exhibits little, if any, association with age.(53,54) Further, results suggest that spine BMD has a positive association with age. This could be due to measurement artifacts (e.g., degenerative changes in the lumbar spine) that are known to obscure AP spine measurements. It is a limitation that this study did not perform lateral spine scans.

Additionally we note that there is an association between FE2 and BMD in the hip but not BMD in the wrist or spine. This could be due to a number of factors including a possible difference in the effect of FE2 on trabecular versus cortical bone. Not surprisingly, grip strength shows a strong relationship with wrist BMD but not with hip or spine BMD. Several other factors are selectively associated with BMD at different sites, including caffeine intake, chronic lung disease, and CTx; the explanation for these findings is not readily apparent.

Similar analyses of spine and hip BMD were previously published by MrOS.(33) The MrOS study and our analyses identify a similar group of variables initially correlated with BMD. In our analyses, we account for a much greater portion of the variance, with R^2 values at 41% at the hip and 24% at the spine compared to 19% and 10% for the MrOS data, respectively. We attribute this difference to the absence of lean mass in their models. When ALM is removed from our model, R^2 drops to 26% at the hip and 16% at the spine. Finally, we note that analyses with MrOS suggest that SSRI use is related to hip and spine BMD.(17,33) Although our

analyses do not show a similar correlation for hip or spine BMD, our results do suggest a correlation between current use of SSRIs and wrist BMD. The potential association between SSRIs and BMD is a relatively new finding and should be explored in future studies.

Results from our analyses using data from the BACH/Bone study provide additional insights into individual factors important for predicting BMD in men and highlight the potential importance of lifestyle changes that might slow age-related declines in BMD. Consistent with the findings from many other studies examining body composition and BMD,(13,55) our results suggest that lean mass is the strongest predictor of BMD in the hip, spine and wrist. Our data also suggest that lowering caffeine intake and increasing physical activity could have a positive impact on BMD. Of course, randomized trials are needed before reaching definitive conclusions about how lifestyle changes can modify BMD or fracture risk.

To date, this report provides one of the most in-depth considerations of the relative contributions to BMD in a large population-based sample of men. The wide range of covariates available for analysis is a clear strength of this study. Not only do we have many variables previously determined to be relevant to BMD, but we can also examine the relative contributions of these factors, rather than their influence in isolation. Furthermore, the probability sampling and the diversity of race/ethnicity and socioeconomic status among participants allows us to consider subjects that otherwise may generally not present for medical care.

Our study also has several limitations. Blood samples were non-fasting and drawn throughout the day and year. In order to control for this variation, we have adjusted for the season and time of blood draw in all models containing markers of skeletal metabolism. Another potential limitation is that some of our risk factors were collected via self-report (i.e., nutrition, smoking, comorbidities), as is typical in epidemiologic studies. We cannot establish causation due to the cross-sectional design, but the design permits us to measure a 'snapshot' of persons in time. While our models may be subject to type I error, our methodology for model selection reduces the potential for it.

Non-participation may affect our estimates. However, the generalizability of the parent BACH Survey from which BACH/Bone is drawn is known. BACH men were similar to men in the National Health and Nutrition Examination Survey, National Health Interview Survey and Behavioral Risk Factor Surveillance Survey with respect to the distributions of common comorbidities (except asthma, more common in BACH).(38,56) Sixty-five percent of eligible BACH men participated in the BACH/Bone study. As previously reported, BACH/Bone participants differed from BACH participants with respect to variables that might impact BMD; in some cases, the effect would be to overestimate average BMD while in others, average BMD might be underestimated.(1) However, as summarized above, many of our identified associations in this analysis have been observed in prior studies. In this analysis, our analytic samples were reduced by missing data. Comparisons of analytic samples to remaining BACH/Bone subjects not in those samples show that the final hip and wrist samples are slightly younger (by ~3 y and ~8 y respectively) t, while the spine sample does not differ by age. The wrist sample contained subjects who have slightly higher ALM than remaining BACH/Bone subjects.

Our findings identify the potential limitations of risk factor epidemiology as a general approach and highlight the need to better understand the relationships in context with other risk factors. In spite of the fact that we have examined many potential risk factors, we are only able to explain about half of the variance in BMD observed in this study, suggesting there may be other risk factors for BMD not included in our study. Nevertheless, our findings contribute to the current literature by suggesting that the most important risk factor for BMD, in the context

of many others, is ALM. Although a causal relationship still needs to be determined, low lean mass is a modifiable risk factor that can be improved with resistance training and physical activity. Therefore, our study may have clinical implications for care and future studies of skeletal health.

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Fig. 1.

Femoral neck (hip) bone mineral density variance. Unexplained and explained variances from R^2 of final model. Percentages for each contributing subgroup calculated using this formula:

$$\frac{\Delta R_i^2}{\sum_{i=1}^7 (\Delta R_i^2)} \times 100$$

. The full model contains: lifestyle (caffeine), function (PASE categories), health (asthma), hormones (free estradiol), age, demographics (education, race/ethnicity), and body composition (height-adjusted appendicular lean mass) subgroups.

Fig. 2.

One-third distal radius (wrist) bone mineral density variance. Unexplained and explained variances from R^2 of final model. Percentages for each contributing subgroup calculated using

$$\frac{\Delta R_i^2}{\sum_{i=1}^5 (\Delta R_i^2)} \times 100$$

this formula: $\sum_{i=1}^5 (\Delta R_i^2)$. The full model contains: age, health (asthma, taking an SSRI, cancer), demographics (race/ethnicity), function (grip strength), and body composition (height-adjusted appendicular lean mass) subgroups.

Fig. 3.

L1-4 bone mineral density variance. Unexplained and explained variances from R^2 of final model. Percentages for each contributing subgroup calculated using this formula:

$$\frac{\Delta R_i^2}{\sum_{i=1}^6 (\Delta R_i^2)} \times 100$$

. The full model contains: lifestyle (caffeine), health (asthma, chronic lung disease), age, serum (season and time of blood draw-adjusted CTx), demographics (race/ethnicity), and body composition (height-adjusted appendicular lean mass) subgroups.

TABLE 1

Weighted^a description of analysis samples

Subgroup	Variables	Femoral Neck (Hip) BMD Sample (N=686)	1/3 Distal Radius (Wrist) BMD Sample (N=985)	Lumbar Spine BMD Sample (N=873)
Age	Age, yr	46.7 ± 12.3	46.5 ± 12.4	47.6 ± 12.6
Demographics	Race/ethnicity ^b			
	Black	27.6%	30.0%	29.0%
	Hispanic	29.9%	32.8%	30.2%
	White	42.6%	37.3%	40.8%
	Education, y	15.5 ± 4.0	15.2 ± 4.0	15.3 ± 4.0
	Income			
	<\$10k	15.4%	14.3%	14.4%
Body Composition	\$10k-29,9k	20.4%	20.1%	22.0%
	\$30k-69,9k	29.3%	34.1%	31.0%
	\$70k +	34.9%	31.5%	32.7%
	Height, cm	176.1 ± 7.4	175.7 ± 7.2	175.6 ± 7.3
	Appendicular lean mass, kg	26.7 ± 4.0	26.8 ± 4.0	26.6 ± 4.0
Hormones	Total fat mass, kg	22.1 ± 8.5	21.9 ± 8.6	22.2 ± 8.8
	Free testosterone, ng/dL ^c	9.1 ± 3.5	9.3 ± 3.6	9.2 ± 3.5
	Free estradiol, pg/mL ^c	0.68 ± 0.26	0.68 ± 0.27	0.68 ± 0.26
	Luteinizing hormone, iu/L ^d	4.4 (3.3, 6.0)	4.4 (3.3, 6.0)	4.5 (3.3, 6.0)
	Follicle-stimulating hormone, iu/L ^d	4.4 (3.1, 6.3)	4.4 (3.0, 6.3)	4.4 (3.1, 6.4)
Lifestyle	Calcium intake ^e	3.1 ± 1.3	3.1 ± 1.3	3.1 ± 1.3
	Caffeine, mg/day	209 ± 155	201 ± 156	203 ± 155
	Protein intake ^e	3.1 ± 1.3	3.0 ± 1.3	3.1 ± 1.3

Subgroup	Variables	Femoral Neck (Hip) BMD Sample (N=986)	1/3 Distal Radius (Wrist) BMD Sample (N=985)	Lumbar Spine BMD Sample (N=873)
	Calorie intake ^e	3.4 ± 1.3	3.4 ± 1.3	3.4 ± 1.3
	Smoking pack years			
	Never smoker	45.5%	47.6%	45.1%
	< 2.5 pack y	14.0%	13.3%	13.8%
	2.5-<10 pack y	13.4%	12.3%	12.4%
	10-<20 pack y	11.9%	11.9%	12.7%
	20+ pack y	15.2%	14.9%	16.1%
	Alcohol			
	0 drinks/day	23.9%	24.5%	25.0%
	< 1 drink/day	36.2%	39.2%	36.6%
	1-3 drinks/day	30.1%	27.7%	28.5%
	3+ drinks/day	9.8%	8.6%	9.9%
	Hours outside per week			
	<1 hr/week	6.3%	6.7%	6.0%
	1-2 hrs	12.3%	14.0%	12.9%
	2-4 hrs	21.4%	21.3%	20.3%
	4-7 hrs	20.4%	20.6%	20.4%
	7+ hrs	39.6%	37.4%	40.4%
	Arthritis	20.8%	17.8%	20.9%
	Cancer	5.5%	5.4%	7.3%
	Family history of broken hip	6.9%	6.2%	6.9%
	Diabetes	7.1%	6.6%	7.7%
	Asthma	15.7%	14.5%	15.1%
	Chronic lung disease	4.8%	3.8%	5.6%
Health	Myocardial infarction	2.3%	3.2%	3.4%
	Stroke	0.5%	1.8%	1.0%
	High cholesterol	25.8%	25.1%	28.1%
	High blood pressure	23.9%	23.1%	25.2%
	Total number of medications			

Subgroup	Variables	Femoral Neck (Hip) BMD Sample (N=686)	1/3 Distal Radius (Wrist) BMD Sample (N=985)	Lumbar Spine BMD Sample (N=873)
	0 medications	18.8%	20.2%	17.9%
	1 medication	19.8%	18.9%	20.2%
	2 medications	18.3%	17.7%	18.2%
	3-4 medications	21.5%	22.6%	21.0%
	5+ medications	21.6%	20.6%	22.8%
	Self-reported health status			
	Excellent or very good	60.8%	58.8%	59.0%
	Good	29.3%	29.8%	29.2%
	Fair or poor	9.9%	11.5%	11.7%
	Thiazides	5.5%	5.5%	5.9%
	Drugs known to increase bone metabolism ^f	10.5%	10.0%	11.4%
	Selective serotonin reuptake inhibitors	7.4%	7.3%	6.7%
Function	Activity (PASE)			
	Low	22.4%	23.1%	23.6%
	Medium	47.1%	48.2%	47.1%
	High	30.5%	28.7%	29.3%
	Mean grip strength, kg	37.7 ± 11.1	37.2 ± 10.8	37.3 ± 10.9
	Physical strength com posite	5.1 ± 1.9	5.1 ± 2.0	5.0 ± 2.0
Serum	Serum calcium , mg/dL ^g	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.4
	Parathyroid hormone, pg/m L ^{d,g}	25.7 (19.1, 35.2)	26.3 (19.3, 36.4)	26.3 (19.6, 36.0)
	Osteocalcin, ng/m L ^{d,g}	4.3 (3.0, 5.7)	4.4 (3.0, 5.7)	4.4 (3.0, 5.7)
	C-terminal telopeptides of Type-1 collagen, ng/m L ^{d,g}	0.39 (0.28, 0.56)	0.40 (0.28, 0.57)	0.39 (0.28, 0.56)
	25-hydroxyvitamin-D, ng/mL ^g	33.9 ± 14.7	34.1 ± 15.0	34.0 ± 15.0
Variables shaded in gray were not significantly related to BMD in age-adjusted linear regression models				

^a All analyses weighted inversely to the probability of selection

^b Un-weighted percentages

^c Conversion factors: free testosterone (to convert to nmol/L, multiply values by 0.0347); free estradiol (to convert to pmol/L, multiply values by 3.671)

^d Due to skewed values these are medians and the 25% and 75% quartiles

^e These variables were divided into quintiles across the entire sample. The numbers presented represent which quintile they fell into by sub-sample (i.e. a 2.5 would signify calcium intake of low to medium intake compared to the rest of the sample)

^f Calcium supplements, vitamin D supplements, and/or anabolic steroids

^g Conversion factors: serum calcium (to convert to mmol/L, multiply values by 0.25); parathyroid hormone (to convert to ng/L, multiply values by 0.1053); osteocalcin & C-terminal telopeptides of Type-I collagen, (to convert to µg/L, multiply values by 1.0); 25-hydroxyvitamin-D (to convert to nmol/L, multiply values by 2.496)

TABLE 2

Results from weighted^a linear regressions of age-adjusted sub-group models and bone mineral density (BMD) in the hip.

Sub-group	Variables	Submodels (N=1,128)			Final Model (N=686)		
		Age-Adjusted β	Standard Error	p	β	Standard Error	p
Age	Age, 10y	-0.034	0.004	<0.001	-0.016	0.005	<0.001
Demographics	Race/ethnicity			<0.001			0.005
	Black	0.088	0.013		0.054	0.017	
	Hispanic	0.003	0.013		0.017	0.015	
	White	ref	--		ref	--	
	Education, y	-0.003	0.001	0.02	-0.004	0.002	0.01
	Race/ethnicity*age			0.008			--
	Black*age	-0.008	0.008		--	--	
Body Composition	Hispanic*age	-0.027	0.009		--	--	
	White*age	ref	--		--	--	
	Height, cm	-0.004	0.001	<0.001	-0.001	0.001	0.22
Hormones	Appendicular lean mass, kg	0.018	0.001	<0.001	0.015	0.002	<0.001
	Free estradiol, pg/ml	0.110	0.027	<0.001	0.058	0.022	0.008
	Follicle-stimulating hormone ^c	-0.018	0.010	0.08	--	--	--
Lifestyle	Caffeine, 100 mg	-0.016	0.003	<0.001	-0.009	0.004	0.01
	Smoking pack yrs			0.03			--
	Never smoker	0.009	0.018		--	--	
	< 2.5 pack y	-0.008	0.021		--	--	
	2.5 - <10 pack y	0.040	0.024		--	--	
	10 - <20 pack y	-0.031	0.021		--	--	

Sub-group	Variables	Submodels (N=1,128)			Final Model (N=686)		
		Age- Adjusted β	Standard Error	p	β	Standard Error	p
Health	20+ pack y	ref	--		--	--	
	Diabetes	0.037	0.018	0.03	--	--	--
	Asthma	-0.029	0.016	0.08	-0.041	0.012	0.001
	Arthritis	0.043	0.012	<0.001	--	--	--
	Cancer	-0.039	0.018	0.03	--	--	--
	Chronic lung disease	-0.043	0.021	0.04	--	--	--
	High blood pressure	0.039	0.013	0.004	--	--	--
	Total number of medications			0.06			
	0 medications	0.047	0.022		--	--	
	1 medication	0.018	0.019		--	--	
	2 medications	0.023	0.018		--	--	
	3-4 medications	-0.002	0.017		--	--	
	5+ medications	ref	--		--	--	
	Grip strength, kg	0.002	0.001	<0.001	--	--	--
	Activity (PASE)			0.06			0.03
Function	Low	-0.044	0.018		-0.042	0.016	
	Medium	-0.015	0.014		-0.021	0.013	
	High	ref	--		ref	--	
Serum	Osteocalcin, ng/mL ^{b,c,d}	-0.021	0.009	0.02	--	--	--

^a All analyses weighted inversely to the probability of selection

^b Natural log transformed

^c Adjusted for season and time of blood draw

^d To convert osteocalcin to $\mu\text{g/L}$, multiply values by 1.0

TABLE 3

Results from weighted^alinear regressions of age-adjusted sub-group models and bone mineral density (BMD) in the wrist.

Sub-group	Variables	Age-Adjusted Coefficient	Submodels (N=1,128)			Final Model (N=992)		
			Standard Error	p	β	Standard Error	p	
Age	Age, 10y	-0.008	0.003	0.003	-0.001	0.003	0.86	
Demographics	Race/ethnicity			<0.001			<0.001	
	Black	0.037	0.006		0.028	0.006		
	Hispanic	-0.012	0.007		<-0.001	0.007		
	White	ref	--		ref	--		
Body Composition	Height, cm	<0.001	<0.001	0.49	0.001	0.001	0.23	
	Appendicular lean mass, kg	0.007	0.001	<0.001	0.004	0.001	<0.001	
	Total fat mass, kg	-0.001	<0.001	0.06	--	--	--	
Lifestyle	Caffeine, 100 mg	-0.003	0.002	0.09	--	--	--	
Health	Diabetes	0.025	0.009	0.006	--	--	--	
	Asthma	-0.014	0.006	0.03	-0.016	0.006	0.008	
	Arthritis	0.022	0.006	<0.001	--	--	--	
	Cancer	-0.015	0.009	0.09	-0.016	0.010	0.09	
	Selective serotonin reuptake inhibitors	-0.024	0.009	0.004	-0.023	0.008	0.005	
	Total number of medications			0.04			--	
	0 medications	0.027	0.009		--	--	--	
	1 medication	0.011	0.009		--	--	--	
	2 medications	0.013	0.008		--	--	--	
	3-4 medications	0.011	0.010		--	--	--	

Sub-group	Variables	Submodels (N=1,128)			Final Model (N=992)		
		Age- Adjusted Coefficient	Standard Error	p	β	Standard Error	p
	5+ medications	ref	--		--	--	
Function	Grip strength, kg	0.002	<0.001	<0.001	0.001	<0.001	<0.001
Serum	25-hydroxyvitamin-D, ng/mL ^{b,c}	<-0.001	<0.001	0.09	--	--	--

^a All analyses weighted inversely to the probability of selection

^b Adjusted for season and time of blood draw

^c To convert 25-hydroxyvitamin-D to nmol/L, multiply values by 2.496

TABLE 4

Results from weighted^a linear regressions of age-adjusted sub-group models and bone mineral density (BMD) in the spine.

Sub-group	Variables	Submodels (N=1,128)			Final Model (N=873)		
		Age-Adjusted β	Standard Error	p	β	Standard Error	p
Age	Age, 10y	0.009	0.005	0.07	0.018	0.005	<0.001
Demographics	Race/ethnicity			<0.001			<0.001
	Black	0.073	0.013		0.064	0.015	
	Hispanic	-0.041	0.014		-0.009	0.016	
	White	ref	--		ref	--	
	Race/ethnicity*age			0.002			--
	Black*age	0.001	0.009		--	--	
	Hispanic*age	-0.031	0.009		--	--	
Body Composition	White*age	ref	--		--	--	
	Height, cm	0.001	0.001	0.55	0.001	0.001	0.36
Hormones	Appendicular lean mass, kg	0.013	0.002	<0.001	0.010	0.002	<0.001
	Free estradiol, pg/ml	0.064	0.031	0.04	--	--	--
Lifestyle	Caffeine, 100 mg	-0.015	0.004	<0.001	-0.009	0.004	0.02
Health	Diabetes	0.039	0.020	0.05	--	--	--
	Asthma	-0.053	0.017	0.001	-0.047	0.013	<0.001
	Chronic lung disease	-0.062	0.020	0.002	-0.048	0.018	0.007
	High blood pressure	0.027	0.015	0.06	--	--	--
Function	Grip strength, kg	0.003	0.001	<0.001	--	--	--

Sub-group	Variables	Submodels (N=1,128)				Final Model (N=873)			
		Age-Adjusted β	Standard Error	p	β	Standard Error	p		
Serum	C-terminal telopeptides of Type-1 collagen ^{b,c,d}	-0.098	0.031	0.001	-0.077	0.028	0.006		

^a All analyses weighted inversely to the probability of selection

^b Natural log transformed

^c Adjusted for season and time of blood draw

^d To convert C-terminal telopeptides of Type-1 collagen to $\mu\text{g/L}$, multiply values by 1.0