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Trajectories of femoral neck strength in relation to the final menstrual period in a multi-ethnic cohort

S. Ishii,

Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

J. A. Cauley,

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A510 Crabtree, Pittsburgh, PA 15260, USA

G. A. Greendale,

Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, Los Angeles, CA 90095, USA

C. J. Crandall,

Department of Medicine/Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at UCLA, 911 Broxton Ave., 1st floor, Los Angeles, CA 90024, USA

M.-H. Huang,

Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, Los Angeles, CA 90095, USA

M. E. Danielson, and

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A532 Crabtree, Pittsburgh, PA 15260, USA

A. S. Karlamangla

Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, Los Angeles, CA 90095, USA

S. Ishii: ishiis-ty@umin.ac.jp

Abstract

Summary—The purpose of this study was to describe the evolution of femoral neck strength relative to load across the menopause transition. It declined significantly over the 10 years bracketing the final menstrual period, and the rate of decline was modified by body mass index, race/ethnicity, and smoking status.

Introduction—Composite indices of femoral neck strength, which integrate dual energy X-ray absorptiometry (DXA)-derived bone mineral density and bone size with body size, are inversely associated with hip fracture risk. Our objective was to describe longitudinal trajectories of the strength indices across the menopausal transition.

Methods—Data came from the Study of Women's Health Across the Nation; participants were pre- or early peri-menopausal, ages 42–53 at baseline, and were followed up for 9.1 ± 1.8 years. Composite indices of femoral neck strength in different failure modes (compression, bending, and

impact) were created in 921 women who had three or more hip DXA scans and had definable final menstrual period (FMP) dates. We used mixed effects models to fit piecewise linear growth curves to the baseline-normalized strength indices as a function of time to/after the FMP.

Results—Compression and impact strength indices did not decline until 1 year prior to the FMP, and declined rapidly thereafter, with some slowing of decline 1 year after the FMP. Bending strength index increased slightly until 2 years prior to the FMP, then plateaued, and began to decline at the FMP. Mean decline in strength indices over 10 years was 6.9 % (compression), 2.5 % (bending), and 6.8 % (impact). Women with higher body mass index had larger declines in two of the three indices. Other major modifiers of rates of decline were race/ethnicity and smoking status.

Conclusions—Femoral neck strength relative to load declines significantly during the menopausal transition, with declines commencing 1 to 2 years prior to the FMP.

Keywords

Composite strength indices; Final menstrual period; Longitudinal trajectory across menopause; Osteoporosis

Introduction

Hip fracture, which represents a major health burden to individuals and to society [1], increases in incidence with age, and its economic impact is expected to rise as life expectancy increases worldwide [2]. Decline in bone mass over time in older adults is a major contributor to this increase in fracture incidence with age. Women experience increases in fracture risk at younger ages than men, and this has been tied to declines in bone mass seen during the menopause transition.

Assessment of bone mass in clinical practice is based on bone mineral density (BMD) measurement by dual energy X-ray absorptiometry (DXA), which provides 2D-projected bone mass per unit area. Longitudinal studies have shown that there is minimal age-related decline in DXA-measured BMD before the peri-menopausal period, and that rapid decline begins around 2 years before the final menstrual period (FMP) [3–5]. Approximately 2 years after the FMP [3–5], BMD decline slows but does not stop. However, there is considerable variation in the rate of decline both during and after the menopause transition [6, 7].

While low BMD is a major risk factor for fracture, measurement of BMD alone is not sufficient to assess fracture risk. Bone structures increase in width as BMD declines with age [8] and this change in bone size can at least partially compensate for declines in BMD [9]. In addition, forces placed on bone during a fall increase in proportion to body weight; thus, a BMD that is adequate to resist fracture in one individual could be inadequate in a heavier one. Greater body weight is associated with less BMD decline during [3, 5, 10] and after the menopause transition [6]. Composite indices of femoral neck strength integrate bone size and body size with BMD to capture the major structural contributions to bone strength relative to loads [11] and represent an improvement over BMD for fracture risk assessment. The composite strength indices are inversely associated with hip fracture incidence in community-dwelling older Caucasian women [11] and can predict fracture risk in the absence of race/ethnicity information as accurately as bone mineral density does when it is supplemented with race/ethnicity information [12]. In addition, the increased fracture risk associated with diabetes is inconsistent with the higher BMD seen in diabetics compared to nondiabetics [13], but is consistent with the lower composite strength indices seen in diabetics relative to nondiabetics [14]. Thus, age- and menopause-related changes in

composite strength indices are more relevant to fracture risk increases during the menopause transition than are changes in BMD alone.

Accordingly, the objectives of this study were to: (1) describe the trajectories of the composite indices of femoral neck strength during the 5 years prior to and 5 years after the FMP in a multi-ethnic cohort of African-American, Caucasian, Chinese, and Japanese women and (2) identify major determinants of the rates of decline in femoral neck strength as the women progress through the transition.

Methods

Study population

Study of Women's Health Across the Nation (SWAN) is a multi-site longitudinal study designed to characterize the biological and psychosocial changes that occur during the menopausal transition in a community-based cohort of 3,302 multi-ethnic women [15]. Criteria for entry included age 42 to 53 years, intact uterus, and at least one ovary; not currently using sex steroid hormone preparations; at least one menstrual period in the 3 months before enrollment; and self-identification as a member of one of five ethnic groups—Caucasian, African-American, Hispanic, Chinese, and Japanese. Participants were enrolled in 1996/1997 at seven clinical sites. Five of the seven sites enrolled a total of 2,413 women, who weighed no more than 136 kg (the maximum allowed on the DXA machines), into the SWAN bone study and obtained DXA scans of the lumbar spine and hip; a total of 46 women from the five bone sites did not meet the weight criterion. All five SWAN bone study sites enrolled Caucasians, and each site also enrolled women belonging to one pre-specified minority ethnic group. All participants were followed up at the SWAN sites annually from baseline (1996/1997) through year 10 (2006/2007). Femoral neck size measurements on archived hip DXA scans were made, as part of the SWAN Hip Strength Sub-Study, on 1,986 women who had a baseline and two or more follow-up hip DXA scans by SWAN visit 10 (2006/2007). For each participant, bone size measurements were made on hip scans from the baseline visit, from the first visit after every change in menopausal transition stage, and from the last SWAN visit, for a total of 6,523 hip scans from 1,986 women. The SWAN parent study and sub-study protocols were approved by the institutional review board at each site, and all participants gave written informed consent.

Those who were lost to follow-up before their menopause, or had hysterectomy and/or bilateral oophorectomy before natural menopause, or used medications that affect ovarian function (sex steroid hormone preparations, gonadotropin-releasing hormone agonists, aromatase inhibitors, selective estrogen receptor modulators) in the 12 months prior to their reported FMP, were excluded from our analysis, leaving an analytic sample of 3,493 hip scans from 921 women (406 Caucasian, 254 African-American, 126 Chinese, and 135 Japanese).

Measurements

At baseline, standardized questionnaires were used to obtain the following information: age (years), race/ethnicity, levels of physical activity (assessed with a modified Baecke interview which provides a summary score of active living, home and recreational physical activity [16, 17]), smoking history (current, ex-smoker, or never smoking), use of sex steroid hormone therapy (estrogen, progestogen, or combination), osteoporosis therapy (bisphosphonates, selective estrogen receptor modulators, calcitonin, and/or parathyroid hormone), medications that affect bone adversely (aromatase inhibitors, antiepileptics, cancer chemotherapy, and corticosteroids—oral and/or inhaled), and use of vitamin D and calcium supplements. Information on use of prescription medications and vitamin D and

calcium supplements was also obtained during follow-up annual visits using interviewer-administered questionnaires.

Height and weight were measured annually using a fixed stadiometer and a digital scale with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters).

Ascertainment of final menstrual period

At baseline and during each annual follow-up visit, participants reported frequency and regularity of menstrual bleeding since the previous visit. A menstrual period is considered final only if the woman has been followed up for 12 months after the date of the index period and has not had any further menstrual bleeding since, in the absence of factors that alter or obscure menstrual bleeding patterns such as pregnancy, breastfeeding, hysterectomy without bilateral oophorectomy prior to the index period, or use of exogenous sex steroid hormone preparations.

Measurement of BMD and bone size

Femoral neck BMD (in gram per square centimeter) was measured annually using Hologic DXA scanners (Hologic, Inc., Waltham, MA) and OsteoDyne's Hip Positioner System (Osteodyne, Inc., Research Triangle Park, NC). Three sites used Hologic 4500A models throughout. Two sites upgraded from 2000 to 4500A models at follow-up visit 8. These sites scanned 40 women on both their old and new machines to develop cross-calibration regression equations. A standard quality control program, conducted in collaboration with Synarc, Inc., included daily phantom measurements, 6-month cross-calibration with a circulating anthropomorphic spine standard, local site review of all scans, central review of scans that met problem-flagging criteria, and central review of a 5 % random sample of scans. Short-term in vivo measurement variability in femoral neck BMD was 0.016 g/cm² (2.2 %). Measurements of femoral neck axis length (FNAL) and femoral neck width (FNW) were made on the DXA scanner monitor using pixel sizes provided by the manufacturer. FNAL is the distance along the femoral neck axis from the lateral margin of the base of the greater trochanter to the apex of the femoral head. FNW is the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis [18].

Computation of hip strength indices

Composite indices of femoral neck strength are designed to capture the femoral neck's ability to withstand load during a fall and derived from DXA-derived femoral neck bone size (FNAL and FNW) and BMD and body size using the following formula [11]:

$$\begin{aligned}\text{Compression strength index (CSI)} &= \frac{\text{BMD} \times \text{FNW}}{\text{weight}} \\ \text{Bending strength index (BSI)} &= \frac{\text{BMD} \times \text{FNW}^2}{\text{FNAL} \times \text{weight}} \\ \text{Impact strength index (ISI)} &= \frac{\text{BMD} \times \text{FNW} \times \text{FNAL}}{\text{height} \times \text{weight}}\end{aligned}$$

All three indices were recorded in units of gram per kilogram meter. With BMD measured in gram per square centimeter, FNW and FNAL in centimeter, weight in kilogram, and height measured in meter, CSI and BSI need to be scaled by 100 to get values in units of gram per kilogram meter. CSI reflects the ability of the femoral neck to withstand an axial compressive load, BSI reflects its ability to withstand bending forces, and ISI reflects the ability of the femoral neck to absorb the energy of impact in a fall from standing height. Buckling ratio, a measure of the susceptibility of cortical long bone to buckle under axial compressive loads (like a straw), is the ratio of the outer radius to cortical thickness [19].

Buckling ratio index (BRI), proportional to the femoral neck's buckling ratio, was computed as the ratio of FNW to femoral neck BMD.

To examine reproducibility, 20 women volunteers were scanned twice on the same day with repositioning, and femoral neck BMD, FNW, and FNAL were measured twice. Intraclass correlation coefficients for the three composite strength indices were all greater than 0.98.

Statistical analysis

Estimation of the trajectories of each strength index was done in three steps: (1) determining the functional form of the mean trajectory using nonparametric locally weighted scatterplot smoothing (LOESS) regression on time from FMP, (2) determining the best location for inflection points (knots) where trajectory slopes change, and (3) piecewise linear, mixed effects regression (with fixed knots) to estimate slopes in each phase and the associations of postulated factors with slopes.

In step 1, after excluding women who reported use of osteoporosis therapies and/or bone-adverse medications any time during the study ($n=350$) and excluding observations more than 5 years from FMP (because of sparseness of data), we used the nonparametric LOESS method to fit a smooth curve to the repeated measures of the composite strength index as a function of time from FMP (Fig. 1). The LOESS plots revealed that the trajectory of each strength index was piecewise linear with two inflection points: one around 1 to 2 years before the FMP and one around the FMP to 1 year after the FMP (Fig. 1).

In steps 2 and 3, we used mixed effects regression to fit piecewise linear models to repeated measurements of each strength index (in separate models) as functions of time from FMP, with three linear segments and 2 knots. This divides the bone strength trajectory in the 10-year period centered at the FMP into three distinct phases: pre-transmenopause (before the first knot), transmenopause (between the first and second knots), and later-postmenopause (after the second knot). To account for within-woman correlation between repeated observations, we included random effects for the intercept and the three slopes (allowing the intercept and slopes to vary from woman to woman). In step 2, we tested model adequacy and appropriateness of knot locations by running null models with only random effects and no fixed effects, varying the locations of knots, and examining the residuals unexplained by the model. The residuals were minimized when the two knots were placed at 1 year prior to FMP and 1 year after FMP for CSI and ISI and 2 years prior to FMP and at FMP for BSI. The residual variance was lowest (as a fraction of total variance) for models with baseline-normalized indices as outcome, compared to models with un-normalized, absolute values of the indices and models with log-transformed indices; therefore, we chose to model baseline-normalized indices as outcomes.

In step 3, with knots fixed at the locations determined in step 2, we added age at FMP, race/ethnicity, smoking status at baseline (current, ex-smoker, or never smoker), physical activity at baseline (dichotomized at median), BMI (continuous), sex steroid hormone therapy (yes/no), osteoporosis therapy (yes/no), use of bone-adverse medications (yes/no), calcium supplementation (yes/no), vitamin D supplementation (yes/no), DXA scanner type, and study site as fixed effects on the intercept and the three slopes and included the baseline value of the index as fixed effects on the three slopes. BMI, prescription medication use, and supplement use were measured annually, and DXA scanner type changed over the study period at two study sites. The baseline values of these covariates were modeled as predictors of the intercept, and their mean value within each of the three phases was used as predictor of that segment's slope. For binary, time-varying covariates such as prescription medication or supplement use, the mean is also the proportion of visits when use was reported. Model

regression coefficients for slopes were combined linearly to get predicted 10-year change in strength indices and the associations of the above factors with the 10-year change.

In secondary analyses, the trajectories of the components of the strength indices (body weight and height, FNW, and FNAL) and of BRI were also each examined using the same three-step approach. All analyses were conducted using SAS version 9.2 and a *p* value less than 0.05 was considered statistically significant.

Results

The study sample ($n=921$) was comparable to the rest of the SWAN Hip Strength Sub-Study cohort with respect to the baseline characteristics, except that women in study sample tended to be lighter, be current smokers, and belong to the minority groups (Table 1). In the study sample, women were followed up for an average of 9.1 (± 1.8) years with 3.8 (± 0.9) available scans.

In the 10 years bracketing the FMP (from 5 years before through 5 years after the FMP), women lost on average 6.9 % of CSI, 6.8 % of ISI, and 2.5 % of BSI. There was no significant change in CSI and ISI until 1 year prior to the FMP; rapid decline in both began at FMP -1 year (Table 2). Decline in both indices slowed statistically significantly 1 year after the FMP. On the other hand, BSI *increased* significantly up to 2 years prior to the FMP, then plateaued, and began to decline at the FMP (Table 2). Of the factors postulated to influence strength trajectories, age at FMP and physical activity at baseline did not have any associations with the trajectories of any of the three strength indices. The influences of other factors were generally consistent across the three composite strength indices.

High BMI was associated with larger decline during transmenopause in all three indices but smaller decline during later-postmenopause in CSI and ISI, resulting in larger reduction in CSI and BSI in the 10 years around the FMP (Table 2). Compared to Caucasians, African-Americans had smaller decline in CSI and ISI during transmenopause and Chinese had smaller decline in the three indices during later-postmenopause. Japanese had smaller decline in CSI and ISI during later-postmenopause but larger decline in CSI during pre-transmenopause and in BSI during transmenopause. As a result, over the 10 years bracketing FMP, Chinese had smaller reduction in CSI and BSI while Japanese had larger reduction in CSI and BSI, relative to Caucasian women (Table 2). However, despite experiencing larger 10-year cumulative loss, Japanese women continued to have higher values of CSI than Caucasian women throughout the 10 years around FMP (see Fig. 2 for model-predicted trajectories of CSI).

Current smokers had larger 10-year declines in ISI while ex-smokers had smaller 10-year declines in CSI compared to nonsmokers (Table 2). Medication use was not associated with total 10-year change in any of the strength indices (Table 2). Higher baseline values of all three indices were associated with greater 10-year reduction (2.8 % per 1 SD increment in the baseline value for CSI, 2.9 % for ISI, and 3.1 % for BSI).

Secondary analyses of trajectories of the components of the composite strength indices and of BRI found that FNW increased linearly with age (without an inflection point), body weight increased in a piecewise linear fashion with one inflection point at FMP, and BRI increased in a piecewise linear fashion with two inflection points, one at FMP -2 year, and one at FMP (Fig. 3). On the other hand, there was minimal to no change in body height and FNAL (less than 1 % over the 10-year period bracketing the FMP). FNW increased at 0.38 %/year on average, for a total increase of 3.8 % over the 10-year period, but Japanese women had a significantly smaller increase (Table 3). Mean rate of increase in body weight

was 0.6 % of baseline weight per year until 1 year after the FMP, then it increased by 0.2 % per year, for mean total increase over 10 years of 4.0 %; Japanese and Chinese women had a significantly smaller weight gain over 10 years around FMP (Table 3). BRI increased by 0.2 % of baseline value each year until 2 years prior to the FMP, by 2.0 % each year over the next 2 years, then 1.9 % each year after FMP. Mean total increase in BRI over 10 years was 13.9 %; there were no significant race/ethnicity differences in increase in BRI (Table 3).

Discussion

Composite indices of femoral neck strength combine femoral neck areal bone density and femoral neck bone size with body height and weight to quantify bone strength relative to three different types of loads: compression, bending, and impact. In this cohort study of middle-aged women from four ethnic groups, we found that, similar to the trajectory of areal bone density over the menopause transition [3, 5], trajectories of the compression and impact strength indices also had three distinct phases: minimal decline in the pre-transmenopause, rapid decline in the transmenopause, and decelerated but continued decline in the later-postmenopause. In contrast, the trajectory of bending strength had a different functional form: It increased gradually in the pre-transmenopause, plateaued in the transmenopause period, and declined in the later-postmenopause. Because of the increase in bending strength in the pre-transmenopause, the 10-year cumulative loss in bending strength was smaller than that in compression and impact strength (2.5 vs. 6.9 and 6.8 %, respectively.)

Differences among trajectories of strength indices to resist specific type of loads may be partly explained by the protective effect of changes in the width of the femoral neck because femoral neck width contributes more to bending strength than it does to the other two indices. Unlike CSI and ISI, BSI is proportional to the *square* of FNW. Age-related femoral neck width increase in adults is the result of periosteal apposition, the compensatory deposition of bone on the outer (periosteal) surface to offset the loss of bone from the inner (endocortical) surface [20–22]. In SWAN, femoral neck width increased even before the commencement of rapid bone loss; this translates into pre-transmenopause *increase* in bending strength, but not in compression or impact strength. In addition, body weight also increased over the study period. Since body weight is in the denominator of the composite indices, an increase in body weight over the menopause transition translates to reductions in all three composite strength indices. Increases in FNW could only partially compensate for the reduction in compression and impact strength caused by increases in body weight and decreases in BMD.

Our study demonstrated that higher baseline values of the strength indices were associated with faster decline during the menopause transition. Importantly, this finding emerged after the indices were normalized by baseline values, suggesting that women with greater bone strength before the menopause transition experience greater decline in strength in both absolute and relative terms.

This study also found that BMI, race/ethnicity, and smoking status are important determinants of the longitudinal trajectory of bone strength although effects on slopes were not significant in all phases of the menopause transition. Women with higher BMI experienced significantly faster declines in strength in transmenopause but slower declines in later-postmenopause and as a result larger strength reduction in aggregate over the 10 years of observation. Although previous studies have shown that higher BMI is associated with slower decline in bone density over time [3, 5, 10], our findings suggest that women with higher BMI, in fact, lose more bone strength relative to load over the menopause transition. Previous studies have also shown that obese women, despite having higher BMD

than non-obese women, actually have lower BMD relative to load [23]. This and our finding of greater decline over time in bone strength relative to load in women with higher BMI are both consistent with recent reports of higher risk of lower extremity fracture in obese women [23, 24].

Compared to Caucasians, African-American women had slower declines during transmenopause and Chinese women had smaller declines during later-postmenopause and smaller cumulative 10-year loss. These two minority groups had also higher values for all three indices than Caucasians at baseline [18], consistent with previously reported lower fracture risk in Chinese and African-American women [25–27]. Japanese women had faster declines during the pre-transmenopause and transmenopause, but significantly slower decline in later-postmenopause. Since they started with significantly higher values at baseline [18], they had higher values of CSI at the end of the 10 years bracketing FMP despite having larger 10-year cumulative loss. Given their significantly slower decline in later-postmenopause, Japanese women may continue to have long-term structural advantage, consistent with previously reported lower fracture risk in elderly Japanese women [26–28].

Race/ethnicity differences in femoral neck strength trajectories were partly due to race/ethnicity differences in femoral neck width. Increases in neck width were smallest in Japanese women, which is also the group with the largest 10-year decline in strength indices. Race/ethnicity differences in trajectories of cortical bone width have not been previously examined, and the finding of smaller increases in femoral neck width in Japanese women warrants further investigation.

With regard to the femoral neck's buckling ratio, an important measure of cortical bone susceptibility to fracture [29], we found that it increased significantly during the menopause transition, and that the cumulative 10-year change in buckling ratio index did not differ among the four race/ethnic groups.

Current smoking was associated with larger cumulative 10-year declines in strength indices, concordant with the detrimental effects of smoking on BMD and fracture risk [30, 31]. Our finding of less bone loss in past smokers supports previous studies which have demonstrated the reversibility of smoking-associated reduction in bone mass [31, 32]; we speculate that past smokers showed smaller declines in bone strength during the menopause transition because they were in the process of recovering previously lost bone mass.

Our study has several important limitations. The composite indices of hip strength employed in this study are structural measures based on macroscopic measurements from DXA scans and ignore microscopic features such as differences in the quality of cancellous mineralization and micro-architecture [33, 34]. We also made the simplifying assumption that mineral mass in the femoral neck is largely in the cortex since details of bone composition are not readily available from DXA scans; however, cross-validation with 3D quantitative computed tomography (QCT)-based strength measures confirm the validity of these DXA-based measures [35], which are also more readily obtainable with substantially less radiation exposure and lower costs than QCT. Although the composite strength indices have not been validated against laboratory measures of mechanical strength, they have been shown to be inversely associated with fracture risk in multiple studies [11, 12, 36, 37]. Lastly, more than half of the participants in the Hip Strength Sub-Study cohort were not included in the longitudinal analysis because they did not have definable FMP dates. The most common reason for exclusion was the use of hormone therapy prior to menopause, which obviates the ability to determine when the natural FMP date occurs. Although we do not have direct information on the indications for hormone therapy use, it was most likely prescribed for vasomotor symptoms. Because there is a small, negative association between

vasomotor symptoms and bone density, it is plausible that the exclusion of hormone therapy users resulted in a study sample with higher than average BMD at baseline [38]. Despite these limitations, this study is, to our knowledge, the first study to describe longitudinal trajectories of femoral neck strength relative to load during the menopause transition. It demonstrated that although bone size increases to partly compensate for declines in bone density, body weight also increases, so that femoral neck strength relative to load declines significantly over the 10 years around the FMP. Declines in strength indices were greater in women who smoked and in those with higher body mass index, offering further support that smoking cessation and maintenance of ideal body weight should be advised clinically. As SWAN has previously reported for BMD, the decline in femoral neck composite strength indices began 1 to 2 years *prior* to the FMP, when more than 70 % of women were still classified as early menopausal by bleeding criteria [5]. Future research should consider whether greater transmenopausal declines in strength indices portends worse fracture outcomes and, if so, whether short-course interventions administered during the transmenopausal period may help preserve long-term skeletal health.

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Clinical Centers University of Michigan, Ann Arbor—Siobán Harlow, PI 2011–present; MaryFran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA—Joel Finkelstein, PI 1999–present; Robert Neer, PI 1994–1999; Rush University, Rush University Medical Center, Chicago, IL—Howard Kravitz, PI 2009–present; Lynda Powell, PI 1994–2009; University of California, Davis/Kaiser—Ellen Gold, PI; University of California, Los Angeles—Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY—Carol Derby, PI 2011–present, Rachel Wildman, PI 2010–2011; Nanette Santoro, PI 2004–2010; University of Medicine and Dentistry—New Jersey Medical School, Newark—Gerson Weiss, PI 1994–2004; and the University of Pittsburgh, Pittsburgh, PA—Karen Matthews, PI.

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Central Laboratory University of Michigan, Ann Arbor—Daniel McConnell (Central Ligand Assay Satellite Services).

Coordinating Center University of Pittsburgh, Pittsburgh, PA—Kim Sutton-Tyrrell, Co-PI 2001–present; Maria Mori Brooks Co-PI 2012; New England Research Institutes, Watertown, MA—Sonja McKinlay, PI 1995–2001.

Steering Committee Susan Johnson, Current Chair

Chris Gallagher, Former Chair

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Fig. 1. LOESS plots of femoral neck composite strength indices as a function of time to and from the final menstrual period (FMP). Abbreviations: *CSI* compression strength index, *BSI* bending strength index, *ISI* impact strength index, *FMP* final menstrual period

Fig. 2.

Model-predicted mean trajectories of the compression strength index in the four race/ethnicity groups. All the other covariates are set to either the sample mean, if a continuous variable (e.g., age at FMP and BMI), or reference category, if a categorical variable (e.g., never smoker, less than median physical activity, not using medications or supplements). The values at 5 years prior to FMP were estimated using multiply-adjusted mean of compression strength index in each race/ethnic group at baseline. *FMP* final menstrual period

Fig. 3. LOESS plots of femoral neck width, body weight, and buckling ratio index as a function of time to and from the final menstrual period (FMP). Abbreviations: *FNW* femoral neck width, *BRI* buckling ratio index, *FMP* final menstrual period

Table 1

Descriptive statistics of study participants

Characteristics	Analysis sample (n=921)	Rest of the hip strength sub-study (n=1,065)
Baseline		
Age (year)	46.3 (2.6)	45.5 (2.7)
Height (cm)	161.7 (6.8)	162.9 (6.3)
Weight (kg)	71.6 (19.6)	73.6 (19.2)
Body mass index (kg/m ²)	27.3 (6.9)	27.6 (6.8)
Menopause status		
Early perimenopause (%)	44.3	42.8
Premenopausal (%)	56.7	57.2
Smoking status		
Current smokers (%)	16.3	13.6
Past smokers (%)	25.0	26.2
Never smokers (%)	58.7	60.1
Physical activity		
More active (%)	49.9	51.7
Less active (%)	50.1	48.3
Race/ethnicity		
African-American (%)	27.6	25.2
Chinese (%)	13.7	9.4
Japanese (%)	14.7	10.5
Caucasian (%)	44.1	54.9
Femoral neck areal bone mineral density (g/cm ²)	0.83 (0.14)	0.85 (0.13)
Femoral neck axis length (cm)	17.9 (1.0)	18.0 (1.0)
Femoral neck width (cm)	2.7 (0.2)	2.8 (0.2)
Compression strength index (g/kg-m)	3.3 (0.7)	3.3 (0.6)
Bending strength index (g/kg-m)	1.02 (0.23)	1.02 (0.21)
Impact strength index (g/kg-m)	0.18 (0.04)	0.18 (0.04)
Buckling ratio index (g/cm ³)	0.31 (0.05)	0.31 (0.05)
Follow-up		
Duration of follow-up (year)	9.1 (1.8)	8.2 (2.9)
No. of hip scans analyzed for bone size	3.8 (0.9)	2.8 (1.0)
Age at final menstrual period (year)	51.5 (2.5)	—
Use of medication at any point during follow-up (%)		
Exogenous sex steroid therapy ^a	8.3	66.2
Osteoporosis medications ^b	10.4	11.6
Bone-loss inducing medications ^c	27.7	36.2
Supplementary vitamin D	64.4	65.5
Supplementary calcium	80.5	81.8
Annual percent change in BMI (%/year)	0.55 (1.30)	0.72 (1.51)

Mean and standard deviation are shown for continuous variables and percentages for categorical variables

^a Exogenous sex steroid therapy include estrogen, progesterone, birth control pills, ovulation stimulators, and gonadotropin-releasing hormone analogs

^b Medications used to treat osteoporosis, including bisphosphonates, selective estrogen receptor modulators, calcitonin, prescription vitamin D, parathyroid hormone, and receptor activator of nuclear factor kappa-B ligand inhibitors

^c Bone loss-inducing medications include oral and inhaled steroids, chemotherapy, antiepileptics, and aromatase inhibitors

Table 2

Factors that influence the trajectories of femoral neck composite strength indices during the menopause transition

Compression strength index	Rate of change (slope ^b) in each FMP-defined phase (%/year)			Predicted 10-year change ^b (%)
	Pre-transmenopause (prior to FMP -1 year)	Transmenopause (FMP -1 year to FMP +1 year)	Later-postmenopause (after FMP +1 year)	FMP -5 years to FMP +5 years
	Mean ^a , 0.03	Mean ^a , -1.92***	Mean ^a , -0.81*** ^g	Mean ^a , -6.93***
Age at FMP (year)	0.02	0.01	0.02	0.16
Body mass index (kg/m ²) ^g	0.02	-0.19***	0.03*	-0.16*
Race ^c				
African-American	-0.37	1.15*	0.21	1.68
Chinese	0.20	-0.74	0.93***	3.04**
Japanese	-0.56*	-1.33	0.50*	-2.86**
Baseline smoking status ^d				
Current smoker	-0.06	-0.79	0.09	-1.48
Ex-smoker	0.25	0.04	0.14	1.63*
Physical activity at baseline ^e	0.03	-0.73	0.25	-0.35
Medications ^{f,g}				
Vitamin D	-0.96*	0.27	0.32	-2.00
Calcium	0.43	-0.28	-0.04	0.97
Exogenous sex steroid therapy	2.14	-1.00	0.41	8.20
Osteoporosis medications	1.09	0.06	0.40	6.09
Bone-adverse medications	-0.03	0.38	0.07	0.94
Impact strength index	Rate of change (slope ^b) in each FMP-defined phase (%/year)			Predicted 10-year change ^b (%)
	Pre-transmenopause (prior to FMP -1 year)	Transmenopause (FMP -1 year to FMP +1 year)	Later-postmenopause (after FMP +1 year)	FMP -5 years to FMP +5 years
	Mean ^a , -0.02	Mean ^a , -1.99***	Mean ^a , -0.68*** ^g	Mean ^a , -6.79***
Age at FMP (year)	0.02	0.04	0.03	0.25
Body mass index (kg/m ²) ^g	0.02	-0.19***	0.04**	-0.13
Race ^c				
African-American	-0.41	1.13*	0.31	1.83
Chinese	-0.12	-0.89	1.12***	2.21
Japanese	-0.40	-1.13	0.75**	-0.87
Baseline smoking status ^d				
Current smoker	-0.01	-1.20	-0.01	-2.47*
Ex-smoker	0.20	0.07	0.20	1.72
Physical activity at baseline ^e	0.07	-0.61	0.21	-0.12
Medications ^{f,g}				

Impact strength index	Rate of change (slope ^b) in each FMP-defined phase (%/year)			Predicted 10-year change ^b (%)
	Pre-transmenopause (prior to FMP -1 year)	Transmenopause (FMP -1 year to FMP +1 year)	Later-postmenopause (after FMP +1 year)	FMP -5 years to FMP +5 years
	Mean ^a , -0.02	Mean ^a , -1.99***	Mean ^a , -0.68*** ^g	Mean ^a , -6.79***
Vitamin D	-0.74	0.14	0.36	-1.21
Calcium	0.43	-0.48	-0.02	0.72
Exogenous sex steroid therapy	1.24	-1.05	0.25	3.87
Osteoporosis medications	1.73	-0.06	0.75	9.78
Bone-adverse medications	0.06	0.38	0.13	1.52

Bending strength index	Rate of change (slope ^b) in each FMP-defined phase (%/year)			Predicted 10-year change ^b (%)
	Pre-transmenopause (Prior to FMP -2 year)	Transmenopause (FMP -2 year to FMP)	Later-postmenopause (After FMP)	FMP -5 years to FMP +5 years
	Mean ^a , 0.34* 0.01	Mean ^a , -0.14	Mean ^a , -0.65***	Mean ^a , -2.52***
Age at FMP (year)		-0.05	0.01	-0.03
Body mass index (kg/m ²) ^g	0.02	-0.15**	0.01	-0.21
Race ^c				
African-American	-0.22	0.39	0.32	1.73
Chinese	0.44	-0.27	0.91*	5.32**
Japanese	-0.69	-2.92**	0.10	-7.41***
Baseline smoking status ^d				
Current smoker	0.001	-0.96	0.30	-0.43
Ex-smoker	0.14	0.65	-0.07	1.35
Physical activity at baseline ^e	0.08	-0.83	0.03	-1.26
Medications ^{f,g}				
Vitamin D	-2.03*	-0.52	0.45	-4.85
Calcium	1.20*	-0.62	-0.25	1.10
Exogenous sex steroid therapy	5.50	-1.36	1.16	19.56
Osteoporosis medications	0.41	-0.02	-0.01	1.17
Bone-adverse medications	0.15	-0.30	0.18	0.77

The mean values of trajectory parameters are from a null model and shown for reference. The first column shows the effect size of each predictor on the value of the intercept and the next three columns show the effect size on the rate of change (slope) in the three periods (pre-transmenopause, transmenopause, and postmenopause periods). All effect sizes are adjusted for all other variables listed in column 1 as well as baseline value of the index, clinical study site, and type of DXA scanner used (Hologic 2000 vs. Hologic 4500; time varying). Statistically significant associations ($p < 0.05$) are also italicized

FMP final menstrual period

^a The mean values of trajectory parameters are from a null model (with no predictors) that fit a single common trajectory to the sample

^b Rate of change (slope) and 10-year change in percentage of baseline value of the index of interest. Negative values mean faster decline, and positive values mean slower decline

^c Ref: Caucasian women

^d Ref: No smoking at baseline visit

^e Above median level of physical activity compared to below median

^fRef: no reported use

^gThe mean value of the predictor within each phase was used to determine its effect on the rate of change (slope) in that phase

*
 $p < 0.05$,

**
 $p < 0.01$,

 $p < 0.001$, p values for test of difference from zero or reference

Table 3

Ten-year change (as percentage of baseline value) in femoral neck width, body weight and buckling ratio index during the menopause transition, and race/ethnicity differences

	Femoral neck width^a 10-year change FMP –5 to +5 years Mean^e, 3.82***	Body weight^b 10-year change FMP –5 to +5 years Mean^e, 3.96***	Buckling ratio index^{c,d} 10-year change FMP –5 to +5 years Mean^e, 13.9***
African-American ^f	0.30	0.86	–1.63
Chinese ^f	0.47	–4.32***	0.97
Japanese ^f	–3.12***	–2.64*	–1.78

Statistically significant associations ($p < 0.05$) are also in italics. Negative effects mean greater decline, and positive effects mean less decline, relative to the Caucasian referent

FMP final menstrual period

^a Femoral neck width modeled as a straight linear function of time (no splines). Race/ethnicity differences are adjusted for age at FMP, body mass index, smoking status, physical activity, use of exogenous sex steroid therapy, osteoporosis medications, medications affecting bone strength adversely, calcium, and vitamin D as well as clinical study site and type of DXA scanner used (Hologic 2000 vs. Hologic 4500)

^b Body weight modeled as a piecewise linear function of time to/from FMP, with one knot at FMP. Race/ethnicity differences are adjusted for age at FMP, body mass index, smoking status, physical activity, use of exogenous sex steroid therapy, as well as clinical study site

^c Buckling ratio index modeled as a piecewise linear function of time to/from FMP, with two knots at FMP –2 years and FMP. Race/ethnicity differences are adjusted for age at FMP, body mass index, smoking status, physical activity, use of exogenous sex steroid therapy, osteoporosis medications, medications affecting bone strength adversely, calcium, and vitamin D as well as clinical study site and type of DXA scanner used (Hologic 2000 vs. Hologic 4500)

^d Buckling ratio index=ratio of femoral neck width to areal bone density

^e The mean values of trajectory parameters are provided for reference and are from a null model (with no predictors) that fit a single common trajectory to the sample

^f Ref: Caucasian women

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$, p values for test of difference from zero or reference