association between MetS and physical performance was found in the cross-sectional analysis of a large-scale cohort study of older men, with obesity having the highest regression coefficient on physical performance among five MetS components [37]. Likewise, another large-scale cohort study of older adults found an association between MetS and poor physical performance, with abdominal obesity explaining the largest fraction of the variation in physical performance [38]. Our findings confirmed these previous studies and additionally demonstrated that abdominal obesity may be the main contributing factor for the associations of MetS with sarcopenia and its individual components regardless of sex and age, suggesting that there is a common mechanism underlying the adverse effects of MetS on muscle, for which abdominal obesity may partly be a marker, and that additional factors are at play causing sex- and age-related differences. Visceral fat accumulation, or abdominal obesity, is hypothesized to play an essential role in the development of MetS, given its propensity to cause insulin resistance, chronic inflammation and lower adiponectin levels [39–42]. All these factors may also be involved in the pathophysiological process of development of sarcopenia [6–9,28], and we postulate that abdominal obesity may represent a clinical phenotype that is associated with increased risk of developing both MetS and sarcopenia. This study had several limitations. First, it could not be free of unmeasured or uncontrolled confounders due to its observational nature. In addition, since this study was cross-sectional, we could not infer a causal relationship between MetS and sarcopenia. Low muscle mass is associated with physical inactivity [10] and insulin resistance [43], and therefore could lead to the development of MetS. We speculate that, in reality, sarcopenia and MetS are deeply intertwined and cause adverse effects on each other, leading to frequent co-existence of these two syndromes. Second, medical history, use of medication and food intake were self-reported. Even though we used a standardized questionnaire, reporting bias was possible. Third, we did not collect information on or adjust for food composition such as total calories, which may confound the sarcopenia-MetS association. Finally, since the subjects were exclusively functionally-independent Japanese older adults, our findings may not be able to be generalized to older adults from other racial/ethnic groups.

In conclusion, this study comprehensively examined the associations of MetS with sarcopenia and its individual components in older adults, with particular attention to the modifying effects of sex and age. We demonstrated associations of MetS with sarcopenia, particularly muscle mass and strength. The associations were modified by sex and age, but were mainly driven by abdominal obesity regardless of sex and age. This study adds to the growing knowledge on the adverse effects of MetS on muscle. Further research is needed to elucidate the underlying mechanisms of the sex- and age-related differences in the association between MetS and sarcopenia.

Supporting Information

Table S1 Characteristics of subjects according to sarcopenia status and age in men and women.
(DOCX)

Table S2 Adjusted associations of metabolic syndrome components with individual sarcopenia components.
(DOCX)

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Author Contributions

Conceived and designed the experiments: SI KI MA. Analyzed the data: SI. Contributed reagents/materials/analysis tools: SI. Contributed to the writing of the manuscript: SI. Contributed substantially to revision: SI KI T. Tanaka MA YO T. Tuji KI. Contributed to data collection: SI KI T. Tanaka T. Tuji.

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Original Full Length Article

Parity, lactation, bone strength, and 16-year fracture risk in adult women: Findings from the Study of Women's Health Across the Nation (SWAN)

Takahiro Mori [a,*], Shinya Ishii [b], Gail A. Greendale [c], Jane A. Cauley [d], Kristine Ruppert [d], Carolyn J. Crandall [e], Arun S. Karlamangla [c]

[a] Department of Medicine/Division of General Internal Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba 296-8602, Japan
[b] Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[c] Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, Ste. 2339, Los Angeles CA 90095, USA
[d] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A510 Crabtree Hall, Pittsburgh, PA 15260, USA
[e] 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

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ABSTRACT

Our objective was to examine the associations of lifetime parity and accumulated length of lactation with bone strength in women prior to the menopause transition and fracture risk during and after the transition. Participants were 2239 pre- or early peri-menopausal women from the Study of Women's Health Across the Nation (SWAN), ages 42–53 years at baseline, who had no childbirths after age 42. Bone mineral density (BMD) was measured in the femoral neck and the lumbar spine at the baseline SWAN visit using dual-energy x-ray absorptiometry, and the composite indices of femoral neck strength relative to load (in three failure modes: compression, bending, and impact) were calculated from femoral neck BMD, femoral neck size, and body size. Data on fractures after age 42 were collected for a median follow-up of 15.7 years (interquartile range, 11.4–18.5 years). In multiple linear regressions adjusted for covariates, lifetime parity was associated positively with femoral neck strength relative to load (0.024 standard deviation (SD) increment in impact strength index per childbirth, $p = 0.049$), but accumulated length of lactation was associated negatively with lumbar spine BMD (0.018 SD decrement per every additional 6 months of lactation, $p = 0.040$). In Cox proportional hazards regressions adjusted for covariates, neither parity nor lactation was associated with fracture hazard after age 42. In conclusion, parity and lactation have little impact on peak bone strength prior to menopause, and do not affect fracture risk after age 42 over 16-year follow-up.

Introduction

During the last trimester of pregnancy and while breast feeding, a woman is at risk of losing bone mass to provide adequate calcium for the child's skeletal development [1]. There is a good evidence that, in the short-term, both pregnancy and lactation can cause bone mineral density (BMD) loss of up to 5%, and that there may be a dose-dependent relationship between length of lactation and amount of bone loss [2,3]. However, the long-term effects of parity and lactation on bone health are not clear. Some studies have even found that parity and lactation are associated with higher BMD later in life, while others have reported lower BMD, or no association with BMD [2].

BMD, however, is not the only bone characteristic that affects bone strength. Bone size relative to body size also plays an important role [4–6], and there are some studies suggesting associations between parity or lactation and bone size later in life [7–9]. Both parity and lactation also have long-term consequences on a woman's body weight [10–12]. Greater body weight independently enhances bone reaccrual (via greater skeletal loading) [13], but also leads to higher impact forces on bone in a fall [6,14]. The combined effect of these changes in BMD, bone size, and body size on bone strength relative to load (i.e., relative to fall impact forces) is not known.

The composite indices of femoral neck strength, which integrate body size with femoral neck size and BMD (both measured from dual-energy x-ray absorptiometry [DXA] scans of the hip), gauge femoral neck strength relative to load during a fall [15]. These indices are inversely associated with incident fractures [15,16], and, unlike BMD, can stratify fracture risk correctly between diabetics and non-diabetics [17], and across race/ethnicity groups [18]. In addition, unlike BMD, the composite indices of femoral neck strength relative to load predict fracture risk in middle-aged women without requiring race/ethnicity information [16].

The primary objective of this study was to examine the associations of lifetime parity and cumulative length of lactation with BMD and the composite indices of femoral neck strength relative to load in pre- or

* Corresponding author at: Department of Medicine/Division of General Internal Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba 296-8602, Japan. Tel.: +81 4 7099 1103.
E-mail address: takahiromori@outlook.com (T. Mori).

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early peri-menopausal women between the ages of 42 and 53 years who have completed their child-bearing. A woman's peak bone strength prior to entering the menopause transition is a reliable indicator of her fracture risk later in life [19–21]. The second objective of this study was to examine the associations of parity and lactation with the risk of fracture after age 42. We used longitudinal data from the Study of Women's Health Across the Nation (SWAN) to study these associations.

Materials and methods

Study participants

SWAN is a multi-site, prospective cohort study of the menopausal transition in a community-based sample of 3302 women from one of five ethnic/racial backgrounds in the United States: Caucasian, African-American, Japanese, Chinese, and Hispanic. The eligibility criteria, described in detail elsewhere [22], included ages 42–52 years, intact uterus and at least one intact ovary, not using sex-steroid hormones at the time of screening, at least one menses in the three months before screening, and self-identification as a member of one of the five eligible ethnic/racial backgrounds. Participants were enrolled in 1996–1997 at seven clinical sites in the following areas: Boston, Chicago, Detroit, Pittsburgh, Los Angeles, Newark and Oakland. The Chicago and Newark sites did not perform BMD measurement, and did not contribute to the SWAN bone cohort. Each of the other five sites enrolled Caucasians, and also enrolled women from another ethnic group: African American in Boston, Detroit, and Pittsburgh, Japanese in Los Angeles, and Chinese in Oakland. These women were followed annually for 10 years and then biennially twice (visits 11 and 12) by 2010–11.

Of 2413 participants at the five SWAN Bone Study sites, 2335 were enrolled in the bone cohort at baseline. The main reason for the exclusion was excess body weight; 46 women could not undergo DXA scans because their body weights exceeded the scanners' weight limit of 136 kg. A SWAN ancillary study, the Hip Strength Across the Menopause Transition study, measured femoral neck size using archived hip DXA scans from the 1960 women in the SWAN bone cohort who had a baseline and two or more follow-up scans by follow-up visit 10. From the SWAN bone cohort, we excluded data from one woman who had initiated sex steroid hormones (a SWAN exclusion criterion) between screening and the baseline visit, 32 women who gave birth after age 42 (29 before the SWAN baseline and three after the baseline visit), two women who did not report their age at the time of a fracture after age 42 but before SWAN baseline, 36 women who reported use of tamoxifen either prior to SWAN baseline or at any time during the study, 18 women for whom menopausal transition stage information was missing at the baseline visit, and seven women for whom baseline BMI measurement was missing. The final sample sizes were 2235 for femoral neck BMD analysis, 2022 for lumbar spine BMD analysis, 1881 for analysis of the composite indices of femoral neck strength relative to load, and 2239 for fracture analysis. The SWAN and sub-study protocols were approved by the Institutional Review Board at each site, and all participants gave written informed consent.

Measurements of bone strength

DXA scans were acquired with Hologic instruments (Hologic, Inc., Waltham, MA, USA). At baseline, two sites (Pittsburgh and Oakland) used QDR 2000, and three sites (Boston, Detroit, and Los Angeles) used QDR 4500. OsteoDyne's Hip Positioner System was used at every site. The DXA quality control protocols in SWAN have been previously described [23]. At the baseline visit, the projected (areal) BMD in the femoral neck and the lumbar spine were recorded, and two femoral neck dimensions were measured using the region of interest (ROI) window, which was repositioned and resized by the DXA operator so that a side of the ROI window spanned the geometric measures of interest. Then the pixel locations of relevant window corners were recorded, and used to calculate the relevant distances in millimeters, using pixel dimensions provided by the manufacturer, Hologic, Inc. They were femoral neck axis length (FNAL): 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, and femoral neck width (FNW): the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis (Fig. 1). The composite indices of femoral neck strength relative to load during a fall were created as follows

$$\text{Compression strength index (CSI)} = \text{BMD} * \text{FNW/weight}$$

$$\text{Bending strength index (BSI)} = \text{BMD} * (\text{FNW})^2/(\text{FNAL} * \text{weight})$$

$$\text{Impact strength index (ISI)} = \text{BMD} * \text{FNW} * \text{FNAL}/(\text{height} * \text{weight})$$

CSI reflects the ability of the femoral neck to withstand an axial compressive load proportional to body weight, BSI reflects the ability to withstand bending forces proportional to body weight, and ISI reflects the ability of the femoral neck to absorb the potential energy of impact in a fall from standing height, regardless of the failure mode: compression or bending [15]. While CSI and BSI assume only that forces on the bone are proportional to body weight, ISI accounts for differences in the forces in a fall that result from differences in a woman's height.

Measurements of total length of lactation, and parity

Standardized interview and self-reported questionnaires were used to obtain information about parity and lactation at the baseline visit. For each pregnancy, participants were asked to choose one of the outcomes; livebirth(s), stillbirth, miscarriage, abortion, or tubal/ectopic, and the total numbers of pregnancies leading to livebirth(s) or stillbirth(s) were counted to obtain lifetime parity. For each pregnancy that led to livebirth(s), participants were asked the length of lactation, and cumulative length of lactation was calculated. Missing values of parity ($n = 4$) and lactation ($n = 4$) were counted as zero. For analysis

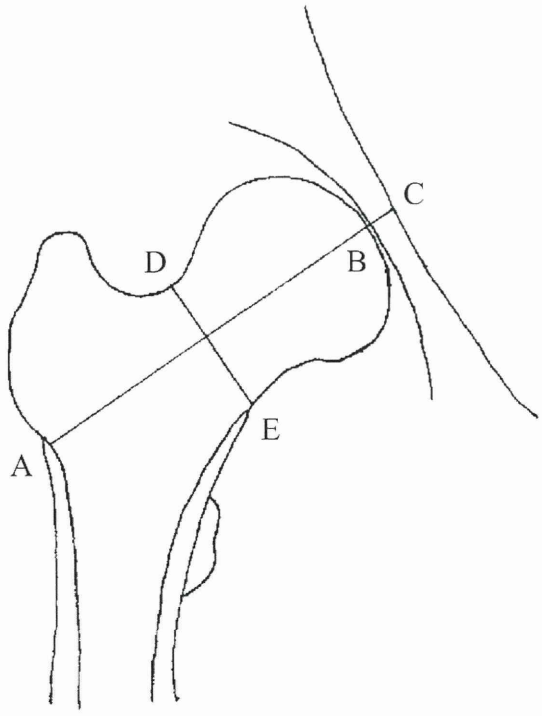

Fig. 1. Femoral neck size measurements. AB is the femoral neck axis length (FNAL): the distance from the base of the greater trochanter to the apex of the femoral head. DE is the femoral neck width (FNW): the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis. C is where the femoral neck axis meets the inner pelvic rim.

as continuous predictors, we top-censored both parity and lactation at their 99th percentiles (6 and 72 months, respectively).

Fracture ascertainment and time to first fracture

At the baseline visit, participants reported prior fractures in adult life, along with their age at the time of the fractures. Because years but not dates of the prior fractures were reported at baseline, we imputed the dates using the midpoints of the year in which the fracture was reported to have occurred. Only fractures after reaching age 42 were included in this analysis. During each of the follow-up visits, fractures since the previous visit were self-reported using a standardized interviewer-administered questionnaire. In all visits, the number of fractures, body site(s) affected, and how fractures occurred were recorded. SWAN initiated collection of the date of fracture at visit 7. Because dates of fractures were not collected in the first 6 follow-up visits, we imputed the dates using the midpoints between the participants' previous and index visits. Medical records were obtained for self-reported non-digital non-cranio-facial fractures reported at visit 7 and later, and 95% were confirmed. Using the 42nd birthday as the start time, we computed time to first fracture after age 42, and censored women who did not report any fracture at their last SWAN visit.

Measurements of covariates

Standardized interview and self-reported questionnaires at baseline were used to obtain the following covariate information: age (continuous; years), race/ethnicity (Caucasian, African-American, Japanese, Chinese), menopause transition stage (premenopausal [regular menses], early perimenopausal [menses within three months but menses less predictable]), smoking status (never smoking, ex-smoker, or current), smoking pack-years (zero, less than or equal to 10 years, greater than 10 years but less than or equal to 30 years, or greater than 30 years), alcohol categories (abstainer, infrequent: greater than zero but less than or equal to one drink per week, light-to-moderate: greater than one but less than or equal to seven drinks per week, heavy: greater than seven drinks per week), employment status (no vs. yes), history of diabetes (no vs. yes), history of hyperthyroidism (no vs. yes), current (i.e., at the baseline visit) use of supplementary calcium, current use of supplementary vitamin D, and six binary indicator variables (none vs. any) for use of medications: 1) prior (i.e., before SWAN baseline) use of any sex steroid hormone pills, patch, or injection other than birth control pills, 2) prior use of birth control pills, 3) prior use of depo-provera injection, 4) current or prior use of oral corticosteroids, 5) current use of proton pomp inhibitors, and 6) use of other bone-adverse medications (including current or prior use of antiepileptic medications, or current uses of chemotherapy, Gonadotropin-releasing hormone agonist, aromatase inhibitors, or thiazolidinediones). At the baseline visit, no one in the bone cohort reported use of osteoporosis medications (bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone, prescription vitamin D, or denosumab).

Medication use information was also collected at every follow-up visit. For fracture analysis, self-reported medication uses from visits 1 to 12 were combined with medication variables collected at the baseline visit to create six indicator variables for ever (prior to baseline, at baseline, or at follow-up) use of medications (none vs. any) from the following classes: 1) sex steroid hormone pills, patch, or injection other than birth control pills, 2) birth control pills, 3) depo-provera injection, 4) oral corticosteroids, 5) proton pump inhibitors, and 6) other bone-adverse medications (defined as described above).

Physical activity was assessed at the baseline visit with an adapted version of the Kaiser Physical Activity Survey, which is based on the Baecke questionnaire [24]. This self-report instrument grades physical activity in four domains: sport, home, active daily living (walking or biking to work, not watching television), and work. Home activity consists of five components: child or dependent adult care, meal preparation and cleanup, light chores such as dusting, moderate chores such as vacuuming, and heavy chores such as home repair. Scores representing the average responses to domain-specific questions range from 1 to 5 for each domain. We calculated a total physical activity score, ranging from 4 to 20, by adding scores across the four domains, with work activity score set at one for those who did not work outside the home [25]. Height and weight were measured at the baseline visit with a fixed stadiometer and a digital scale with the participants wearing light clothing and no shoes. BMI was calculated as weight in kilo grams divided by the square of height in meters.

A total of 369 women (15.8%) had one or more missing covariates at the baseline. We imputed the missing values from values reported in follow-up visits (for menopausal transition stage, height, and alcohol consumption level), and by using default values of never/zero/no for smoking status, smoking pack-years, history of hyperthyroidism, and medications. Those who still had missing values of menopausal transition stage or BMI were excluded from the analysis. Finally the missing values of physical activity score were imputed using predictive mean matching ($n = 74$), as the missingness pattern was monotone [26,27].

Statistical analysis

We performed multiple linear regressions separately to examine the associations of lifetime parity and cumulative length of lactation with each of the bone strength measures (femoral neck BMD, lumbar spine BMD, and the three composite indices of femoral neck strength relative to load) at baseline, adjusted for the following covariates also measured at baseline: age, race/ethnicity, menopausal transition stage, BMI, smoking status, smoking pack-years, alcohol consumption level, physical activity level, employment status, history of diabetes, history of hyperthyroidism, current use of supplementary calcium, current use of supplementary vitamin D, six medication indicator variables: prior use of any sex steroid hormone pills, patch, or injection other than birth control pills, prior use of birth control pills, prior use of depo-provera injection, current or prior use of oral corticosteroids, current use of proton pomp inhibitors, other bone-adverse medications, and study site. We included BMI as a continuous (linear) term, plus a squared (quadratic) term to allow for possible higher-order associations, plus multiplicative interaction terms between BMI and race/ethnicity because of the large race/ethnicity differences in BMI.

In exploratory analysis, we re-ran the models after excluding the BMI terms, or physical activity level and employment status from the regression models. To test for possible effects of parity and length of lactation on bone size, we also ran parallel models with FNW and femoral neck cross-sectional bone mineral content (given by FNW* femoral neck BMD) as the dependent variables (outcomes) [15].

Next, we performed Cox proportional hazards regressions to model time to first fracture (after age 42) as a function of parity or cumulative length of lactation prior to age 42, after we had verified the proportional hazards assumption. We did not distinguish between traumatic and non-traumatic fractures in the analysis, as information regarding the mechanism of fracture (i.e. trauma vs. minimal trauma) was not available for fractures before the SWAN baseline. We excluded factures not typically associated with osteoporosis, in particular fractures of the face, skull, fingers, and toes [28,29]. Women who initiated osteoporosis medications were censored at the time of the first visit in which the participants reported the use. We adjusted for race/ethnicity, select covariates measured at SWAN baseline (BMI, smoking status, smoking pack-years, alcohol consumption level, physical activity level, employment status, history of diabetes, history of hyperthyroidism, supplementary calcium, and supplementary vitamin D), and the following six medication variables as time-invariant covariates: ever use (before baseline or any time during the study till visit 12) of sex steroid hormone pills, patch, or injection other than birth control pills, birth control pills, depo-provera

injection, oral corticosteroids, proton pomp inhibitors, and other bone-adverse medications, and study site.

In sensitivity analysis, we a) included both parity and lactation in the same models to mutually adjust parity for lactation, and lactation for parity, and b) excluded stillbirths from the parity count. Statistical analysis was performed using the STATA Version 13.1 (StataCorp LP, College Station, Texas, U.S.A.). Two-sided $p < 0.05$ was considered significant.

Results

The median age of study participants was 46 years, 49.8% were Caucasian, 28.5% were African American, 11.3% were Japanese, and 10.5% were Chinese. The median and the interquartile range (IQR) of parity were 2, and [1,3] and the mean, the median, and the IQR of cumulative length of lactation were 8.6, 1, and [0, 12] months (Table 1). Pearson's correlation between parity and lactation was 0.38.

Table 1
Characteristics[a] of the study participants at baseline.[b]

Characteristics	Study sample with composite indices of femoral neck strength data ($n = 1881$[c])	Study sample with fracture data ($n = 2239$)
Age (year)	46 [44, 48]	46 [44, 48]
Race/ethnicity		
Caucasian	936 (49.8%)	1115 (49.8%)
African American	499 (26.5%)	637 (28.5%)
Japanese	231 (12.3%)	252 (11.3%)
Chinese	215 (11.4%)	235 (10.5%)
Body mass index (kg/m^2)	25.6 [22.3, 31.1]	26.0 [22.5, 31.6]
Menopausal transition stage		
Premenopausal	1066 (56.7%)	1210 (54.3%)
Early perimenopausal	815 (43.3%)	1017 (45.7%)
Smoking status		
Current	281 (15.1%)	367 (16.5%)
Ex-smoker	475 (25.4%)	570 (25.7%)
Never smoked	1111 (59.5%)	1285 (57.8%)
Smoking pack-year		
0	1190 (64.2%)	1382 (62.7%)
≤10 years	300 (16.2%)	351 (15.9%)
>10 ≤ 30 years	291 (15.7%)	364 (16.5%)
>30 years	74 (4.0%)	108 (4.9%)
Alcohol consumption level		
Abstainer	899 (51.2%)	1074 (51.3%)
Infrequent	391 (22.3%)	459 (21.9%)
Light to moderate	364 (20.7%)	442 (21.1%)
Heavy	101 (5.8%)	120 (5.7%)
History of diabetes	85 (4.5%)	117 (5.2%)
History of hyperthyroidism	68 (3.6%)	81 (3.6%)
Current use of supplementary calcium	844 (44.9%)	988 (44.2%)
Current use of supplementary vitamin D	723 (38.5%)	851 (38.1%)
Medication use; baseline visit		
Prior use of sex steroid hormones (pills, patch, or injection) other than birth control pills	119 (6.4%)	159 (7.1%)
Prior use of birth control pills	1382 (73.8%)	1643 (73.7%)
Prior use of depo-provera injection	13 (0.7%)	18 (0.8%)
Current or prior use of oral corticosteroids	109 (5.8%)	142 (6.3%)
Current use of proton pump inhibitors	24 (1.3%)	29 (1.3%)
Current or prior use of bone adverse medications[d]	50 (2.7%)	57 (2.5%)
Medication use ever (till 12th follow-up)[e]		
Sex steroid hormones (pills, patch, or injection) other than birth control pills	711 (37.8%)	825 (36.8%)
Birth control pills	1423 (75.7%)	1687 (75.3%)
Depo-provera injection	25 (1.3%)	30 (1.3%)
Oral corticosteroids	449 (23.9%)	523 (23.4%)
Proton pump inhibitors	399 (21.2%)	457 (20.4%)
Bone adverse medications[d]	312 (16.6%)	350 (15.6%)
Physical activity score (ranging from 4 to 20)[f]	9.7 [8.4, 11.1]	9.7 [8.5, 11.1]
Home activity score (ranging from 1 to 5)	2.6 [2.2, 3.4]	2.6 [2.2, 3.4]
Employment status	1548 (82.3%)	1914 (82.1%)
Parity and lactation		
Parity (including live births and stillbirths)	2 [1, 3]	2 [1, 3]
Duration of lactation (months)	2 [0, 12]	1 [0, 12]
Bone strength measurements		
Femoral neck bone mineral density (g/cm^2)	0.83 [0.74, 0.92]	0.84 [0.75, 0.93]
Lumbar spine bone mineral density (g/cm^2)	1.06 [0.97, 1.15]	1.07 [0.97, 1.15]
Compression strength index (g/kg-m)	3.28 [2.86, 3.70]	–
Bending strength index (g/kg-m)	1.00 [0.86, 1.15]	–
Impact strength index (g/kg-m)	0.18 [0.16, 0.21]	–

[a] Median and interquartile range for continuous variables and number of participants and percentage for categorical variables.
[b] All characteristics reported were measured at baseline except the 'medication use ever' variables, which were used in the fracture analysis.
[c] Femoral neck size was measured in a subset of women in the Hip Strength Across the Menopause Transition SubStudy. $n = n =$ Sample sizes were greater than 1881 for femoral neck bone mineral density ($n = 2235$) and lumbar spine bone mineral density ($n = 2022$).
[d] Included antiepileptic medications, chemotherapy, gonadotropin-releasing hormone agonist, aromatase inhibitors, or thiazolidinediones.
[e] Any use including either prior or at baseline, or during the follow-up till visit 12.
[f] Sum of four domains of physical activity: sport, home, active living, and work.

Associations with bone strength measures

In multiple linear regressions, parity was positively associated only with ISI and not with any of the other four measures of bone strength (Table 2): Each additional childbirth before age 42 was associated with 0.024 standard deviation (SD) (95% confidence interval (CI): 0.0001, 0.048) increment in ISI ($p = 0.049$). Additional adjustment for length of lactation did not change the point estimate of the parity-ISI association, but the CI widened (95% CI: −0.003, 0.051) and made the association statistically marginally significant ($p = 0.080$). Excluding stillbirths from the parity count also made the association with ISI become marginally significant ($p = 0.059$). Parity also had no association with FNW ($p = 0.66$) or cross-sectional bone mineral content ($p = 0.42$).

Length of lactation was itself inversely associated only with lumbar spine BMD, and not with any of the other four bone strength measures (Table 2): Lumbar spine BMD was 0.018 SD (95% CI; −0.036, −0.001) lower for every additional 6 months of lactation before age 42, ($p = 0.040$). After further adjusting for parity, the inverse association with lumbar spine BMD became weaker (standardized effect size = −0.015 SD) and statistically non-significant ($p = 0.13$). Length of lactation also had no association with FNW ($p = 0.35$) or cross-sectional bone mineral content ($p = 0.52$).

To explore the reasons for the positive association between parity and ISI, and the lack of strong negative associations between parity/lactation and bone strength measures, we examined the associations of parity and lactation with total physical activity level, home physical activity level, and BMI. We speculated that any negative effects of child bearing and lactation on bone health were at least partly negated by the potentially higher home physical activity (child and home care) of child rearing, and its effects on body weight. In multiple linear regressions, both parity and lactation were associated with higher total physical activity level and higher home physical activity level: Each additional childbirth was associated with 0.09 SD (95% CI; 0.06, 0.13, $p < 0.001$) increment in total physical activity score, and every additional 6 months of lactation was associated with 0.06 SD (95% CI; 0.04, 0.08, $p < 0.001$) increment in total physical activity score. In addition, each additional childbirth was associated with 0.20 SD (95% CI; 0.17, 0.23, $p < 0.001$) increment in home physical activity score, and every additional 6 months of lactation was associated with 0.08 SD (95% CI; 006, 0.10, $p < 0.001$) increment in home physical activity score. In multiple linear regressions, parity was associated with higher BMI: Each additional childbirth was associated with 0.32 kg/m^2 (95% CI; 0.13, 0.52, $p < 0.01$) increment in BMI. Lactation was not significantly associated with BMI.

After excluding physical activity level and employment status from the regression models, parity remained positively associated with ISI (effect size before adjusting for lactation: 0.034 SD, 95% CI; 0.010, 0.058, $p < 0.01$), but lactation was no longer negatively associated with lumbar spine BMD. After excluding the BMI terms (but retaining physical activity and employment status), parity was no longer positively associated with ISI, but lactation remained negatively associated with lumbar spine BMD: (effect size before adjusting for parity: −0.019 SD, 95% CI: −0.038, −0.0004, $p = 0.045$). After excluding physical activity level, employment status, and the BMI terms, parity was no longer associated with ISI, and lactation became marginally significantly associated with lumbar spine BMD (effect size before adjusting for parity; −0.017SD, 95% CI: −0.036, 0.001, $p = 0.064$).

Associations with fracture

After a median follow-up of 15.7 years (interquartile range [IQR] 11.4, 18.5), which included median 4.1 years between age 42 and the baseline visit and median 13.2 years of prospective follow-up after the baseline visit, 357 women (15.9%) had at least one fracture, at a rate of 11.0 fractures per 1000 person-years. At visit 12, 1678 (96.8 %) out of 1733 participants had reached post-menopausal status, including those who had a hysterectomy and/or both ovaries removed (175 participants, 10.1%). Median age of natural (non-surgical) final menstrual period was 52 years (IQR 50, 53). In multivariable Cox proportional hazards regressions, neither lifetime parity before age 42 nor accumulated length of lactation before age 42 was associated with the hazard of fracture after age 42. The adjusted relative hazards (with 95% CI) were 0.97 (0.89, 1.05) per additional childbirth and 0.97 (0.92, 1.02) per every additional 6 months of lactation, respectively. The sensitivity analysis (addition of mutual adjustment for parity and lactation, and exclusion of stillbirths from the parity count) did not substantially alter the conclusions of the fracture analysis.

Discussion

Similar to some previous studies [30–33], this study also found that cumulative length of lactation before age 42 was associated inversely with BMD in pre- or early peri-menopausal women ages 42–53 years, but only with BMD in the lumbar spine, not in the femoral neck. Length of lactation was not associated with any of the composite indices of femoral neck strength relative to load. Lifetime parity before age 42 was associated with only one of the three composite indices of femoral neck strength relative to load, and not associated with BMD in either femoral neck or lumbar spine. These two associations (of the ten that were tested) were small: 0.024 SD increment in ISI per childbirth and 0.018 SD decrement in lumbar spine BMD for every 6 months of lactation. In addition, as seen in some previous studies [34–38], neither parity nor lactation was associated with fracture hazard after age 42 (over median 15.7 years of follow-up). Taken together, these findings suggest that parity and lactation have no (or minimal, if any) long-term implications on bone strength and fracture risk.

Table 2
Adjusted[a] associations[b] (with 95 % confidence interval) of lifetime parity (before age 42) and accumulated length of lactation (before age 42) with bone strength measurements at study baseline.

	Femoral neck BMD ($n = 2235$, mean 0.85, SD 0.14)	Lumbar spine BMD ($n = 2022$, mean 1.07, SD 0.13)	Compression strength index ($n = 1881$, mean 3.3, SD 0.64)	Bending strength index ($n = 1881$, mean 1.02, SD 0.22)	Impact strength index ($n = 1881$, mean 0.18, SD 0.04)
Lifetime parity (per childbirth)	0.0002 (−0.025, 0.025)	−0.026 (−0.058, 0.006)	0.022 (−0.002, 0.046)	0.024 (−0.004, 0.051)	0.024* (0.0001, 0.048)
Lactation duration (per every 6 months)	0.002 (−0.012, 0.016)	−0.018* (−0.036, −0.001)	0.007 (−0.007, 0.020)	0.009 (−0.006, 0.024)	0.006 (−0.007, 0.020)

Abbreviations: BMD = bone mineral density, SD = standard deviation.

[a] Multiple linear regressions adjusted for age, race/ethnicity, menopausal transition stage, body mass index, smoking status, smoking pack-years, alcohol consumption level, physical activity level, employment status, diabetes, hyperthyroidism, current use of supplementary calcium, current use of supplementary vitamin D, prior use of sex steroid hormones, prior use birth control pills, prior use of depo-provera injection, current or prior use of oral corticosteroids, current use of proton pump inhibitors, other bone-adverse medications, and study site.

[b] Units: BMD or strength index standard deviation.

* $p < 0.05$.

Any bone mass that may have been lost during pregnancy and breast feeding appears to be regained before a woman enters the menopause transition. This recovery may be partly attributable to higher levels of physical activity in those with higher parity: we found that both parity and lactation were associated with higher total physical activity level and higher home physical activity level, which has beneficial effects on bone health [25]. We also found that parity, not lactation, was positively associated with BMI in later life, which is consistent with previous studies that have shown that parity may be associated with greater body weight in later life, while the long-term effect of lactation on weight appears to be unclear [10–12]. Greater weight enhances bone re-accrual (via greater skeletal loading) [13], which could increase BMD. At the same time, greater body weight increases impact forces during a fall [6,14]. It is, therefore, theoretically possible that the recovery in bone mass is not enough to compensate for the increase in impact forces. We found, however, that the composite indices of femoral neck strength relative to load were *not* lower in women with higher parity or longer length of lactation.

Like ours, another recent study also reported an association between longer length of lactation and lower BMD in the lumbar spine, but not in the femoral neck or the total hip [33]. Compared with femoral neck BMD, lumbar spine BMD has a higher proportion of trabecular bone, which is more metabolically active [39,40], and possibly more susceptible to hormonal influences and reduction in calcium reserves than femoral neck BMD. Although others and we have seen lower BMD in the lumbar spine in women with longer length of lactation, the size of the effect in women approaching the menopause transition is small, and may not impact fracture risk in later life. No study that we are aware of has found that lactation is associated with higher fracture rate in the long-term.

The assumptions and implications of our fracture study design, in particular of not distinguishing between traumatic and non-traumatic fractures, deserve mention. Just like low bone strength is a risk factor for a non-traumatic fracture, it is also a risk factor for a traumatic fracture, in that when there is a trauma, those with lower bone strength are more likely to have a fracture [41]. However, for traumatic fractures to be useful as indicators of osteoporosis (or low bone strength), one has to assume that the occurrence of a trauma is random and not related independently to the predictors of interest (parity and lactation, in this analysis). This is analogous to the assumption made when one examines non-traumatic fractures exclusively, which is that fall risk is not related to the predictors of interest. It is not clear that either assumption is more defensible than the other. Under these two assumptions (note that both are needed here), our study implies that parity and cumulative length of lactation by age 42 are not related to the subsequent hazard of fracture over a median follow-up of 15.7 years.

The limitations of our study need to be acknowledged. Firstly, our assessment of length of lactation could have been affected by recall bias. Previous studies, however, have suggested that long-term recall of length of lactation is reproducible and accurate [42,43]. Secondly, our study was not powered to find small effects on fracture risk. A previous meta-analysis showed that the relative risk of all fractures associated with one SD decrement in lumbar spine BMD is 1.5 [44]; thus, the expected relative increase in risk of fracture per 6 additional months of lactation would be only 0.7%. Thirdly, we did not have information about non-clinical vertebral fractures, which might underestimate the incidence of fractures. The above-mentioned meta-analysis reported that the relative risk of spine fracture associated with one SD decrement in lumbar spine BMD is 2.3 [44]. Fourthly, fractures were self-reported. However, medical records were obtained for 67% of self-reported non-digital non-cranio-facial fractures and 95% were confirmed. Furthermore, the fracture analysis examined time to first fracture after age 42, but covariate data were collected at SWAN baseline, when median age was 46 years. Covariates such as BMI, physical activity level, and alcohol consumption level may have changed from the baseline visit, which may have introduced some bias in findings. In addition, effects of pregnancy after age 42 were not addressed, and effects of adolescent pregnancy were not distinguished. Finally, the cohort was middle-aged and the rate of fractures was low.

Despite these limitations, our study has several strengths, including the multi-site design and size of the study sample, long length (nearly 16 years) of follow-up, assessment of parity and accumulated length of lactation up to the same age (age 42) for every woman and assessment of fractures from that time point forward. In addition, we investigated potential factors that might have contributed to nullify the effects of parity and lactation on bone strength, such as total physical activity level, home physical activity level, and higher BMI. Finally, to our knowledge, this is the first study to examine the associations between parity or lactation and bone strength relative to load. The importance of incorporating bone size and body size into BMD to assess bone strength relative to load has been demonstrated in multiple cohorts [15,16,45–47].

In conclusion, lifetime parity and cumulative length of lactation had few, small associations with bone strength in pre- or early peri-menopausal women. Parity and length of lactation were also not associated with risk of fracture after age 42, over median follow-up of 16 years. This study adds to the accumulating evidence that parity and lactation have no (or minimal, if any) long-term deleterious effects on bone 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.

NIH Program Office: National Institute on Aging, Bethesda, MD — Winifred Rossi 2012–present; Sherry Sherman 1994–2012; Marcia Ory 1994–2001; National Institute of Nursing Research, Bethesda, MD — Program Officers.

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

Coordinating Center: University of Pittsburgh, Pittsburgh, PA — Maria Mori Brooks, PI 2012–present; Kim Sutton-Tyrrell, PI 2001–2012; 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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Authors' roles

Study concept and design: TM, GAG, JAC, CJC, and ASK. Acquisition of data: GAG, JAC, and ASK. Analysis and interpretation of data: TM, SI, and ASK. Drafting manuscript: TM. Revising manuscript content: TM, SI, GAG, JAC, KR, CJC, and ASK. Approving final version of manuscript: TM, SI, GAG, JAC, KR, CJC, and ASK. TM takes responsibility for the integrity of the data analysis.

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Development of conversion formulae between 4-m, 5-m and 6-m gait speed

Dear Editor,

Physical performance is considered an essential component of the definition of sarcopenia and its diagnostic strategy.[1] Recently, the Asian Working Group on Sarcopenia has recommended that 6-m usual gait speed be used for measurement of physical performance.[2,3] Unfortunately, the measurement method of usual gait speed varies considerably by study, minimizing the ability to generalize the study findings. In Japan, 5-m gait speed has been used in several major cohort studies in the elderly.[4–6] In the present study, we aimed to develop conversion formulae between 6-m and 5-m gait speed.

Data were taken from the second year examinations of the Kashiwa study. Briefly, the Kashiwa study is a prospective cohort study on community-dwelling, functionally independent adults aged 65 years or older living in Kashiwa, Chiba, Japan, and the second year examination was conducted between September and November 2013.[5] All 1529 participants who underwent gait speed measurements were included in the analysis (782 men, 747 women). Gait speed measurements were conducted by instructing participants to walk over an 11-m straight course on a flat floor at their usual speed, during which the time was measured for both a 5-m walk (from 3-m to 8-m line) and 4-m walk (from the starting line to 4-m line) during one walk. Gait speed for both measurements was calculated in m/s. The correlation between these two measurements was 0.82.

The non-parametric locally weighted scatter plot smoothing (LOESS) method showed that the relationship between 4-m gait speed and 5-m gait speed was piecewise linear with an inflection point (change of slope) at a 5-m usual gait speed of 1.6 m/s. The piecewise linear model had better fit than a simple linear model, and the change of slope was statistically significant ($P < 0.001$). We also tested if the relationship between 4-m gait speed and 5-m gait speed was modified by sex, but the modification effect was not statistically significant ($P = 0.22$). All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

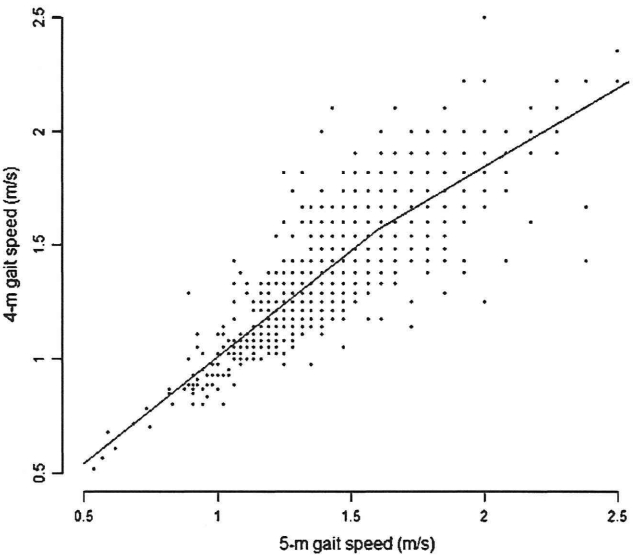

Figure 1 Scatter plot for 4-m gait speed and 5-m gait speed, and fitted piecewise linear relationship.

Participant characteristics (mean ± standard deviation) were: age 73.9 ± 5.5 years, 5-m gait speed 1.52 ± 0.25 m/s and 4-m gait speed 1.48 ± 0.26 m/s. Piecewise linear regression showed that the following equations could be used to convert from 5-m to 4-m gait speed:

For 5-m gait speed ≤1.6 m/s:

$$\text{4-m gait speed} = 0.934 \times (\text{5-m gait speed}) + 0.074$$

For 5-m gait speed >1.6 m/s:

$$\text{4-m gait speed} = 0.69 \times (\text{5-m gait speed}) + 0.463$$

The scatter plot of 4-m and 5-m gait speed, and their piecewise linear relationship are shown in Figure 1. The $R^2 = 0.68$.

To convert to 6-m gait speed, we substituted the aforementioned equations for 4-m gait speed in the formula with the R^2 of 0.93 from a previous study on a

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