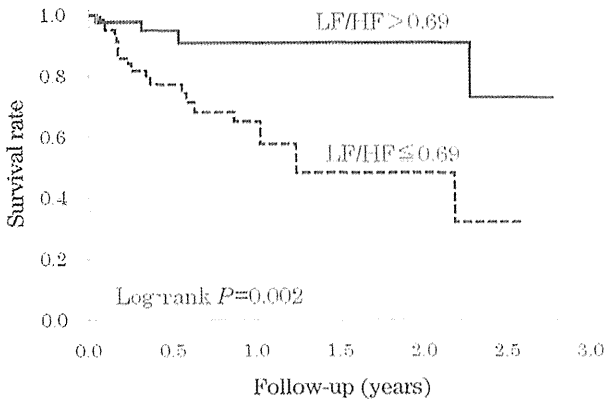


**Figure 2** Kaplan–Meyer survival curves for death according to low frequency/high frequency (LF/HF). Mortality was significantly higher for patients with low LF/HF than for patients with high LF/HF. The mean follow-up period was 8.9 months.

flow and muscle strength by inducing muscle protein synthesis,[34–37] suggesting that low sympathetic nervous activity is related to not only physical dysfunction, but also the inability to maintain muscle strength, leading to a worse outcome in LTC elderly. Appropriate activation of the sympathetic nervous system might prevent muscle wasting and improve overall mortality in LTC elderly.

Activation of the sympathetic nervous system has been applied to aging or sarcopenic model rats. The β2-adrenergic agonists, clenbuterol and formoterol, improved muscle mass and muscle strength, and prevented muscle aging in aging, disuse and sarcopenia[38–44] model rats. In contrast, inhibition of sympathetic nervous activity with β-blockers was associated with a worse outcome in older adults.[45] These findings also suggest the importance of preventing a sympathetic nervous activity decline in LTC elderly.

There were several study limitations. First, this was an observational study, and could not provide direct evidence of causality. So it will be necessary to carry out randomized controlled trials to show whether high sympathetic nervous activity leads to a good outcome or not. Second, excessive sympathetic nervous activity is associated with cardiovascular risk factors, such as hypertension, left ventricular myocardial hypertrophy and old cerebrovascular disease.[46,47] In addition, the number of control subjects was relatively small in the present study. Based on these results, it might be hard to apply the findings in the present study to the oldest old population in general. However, some studies, particularly in the elderly, showed that decreased sympathetic nervous activity was associated with a worse outcome.[9] In addition to low physical activity, poor handgrip strength and frailty are known to be important risk factors predicting death older adults,[2,48–50] and few reports have focused on LTC elderly. Therefore, the present study has the possibility of providing evidence to improve physical function and mortality in LTC elderly by means of maintaining or increasing LF/HF.

In summary, the present study showed that LF/HF is a factor that distinguishes LTC elderly from elderly controls independent of physical function. In addition, the circadian rhythm of LF/HF was lost in LTC elderly. Furthermore, low LF/HF was associated with high mortality. For LTC elderly aged 75 years or over, LF/HF might be a predictive biomarker of physical function and mortality.

## Disclosure statement

There is no financial support or relationship that might pose conflicts of interest.

## References

1 Japanese Ministry of Health, Labor and Welfare. Changes in the number of people certified for long-term care/support need. 2008. [Cited 23 Aug 2011.] Available from URL: http://www.mhlw.go.jp/english/wp/wp-hw3/dL/10-06.pdf
2 Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol* 2001; **56**: M146–M156.
3 Japanese Ministry of Health, Labor and Welfare. Welfare policy for the elderly with a focus on long-term care insurance system. 2007. [Cited 23 Aug 2011.] Available from URL: http://www.mhlw.go.jp/english/wp/policy/dL/04.pdf
4 Camillo CA, Pitta F, Possani HV *et al.* Heart rate variability and disease characteristics in patients with COPD. *Lung* 2008; **186**: 393–401.
5 Muslumanoglu L, Aki S, Turkdogan D, Us O, Akyuz G. Involvement of sympathetic reflex activity in patients with acute and chronic stroke: a comparison with functional motor capacity. *Arch Phys Med Rehabil* 2004; **85**: 470–473.
6 Oka H, Morita M, Onouchi K, Yoshioka M, Mochio S, Inoue K. Cardiovascular autonomic dysfunction in dementia with Lewy bodies and Parkinson's disease. *J Neurol Sci* 2007; **254**: 72–77.
7 Oka H, Yoshioka M, Morita M *et al.* Reduced cardiac 123I-MIBG uptake reflects cardiac sympathetic dysfunction in Lewy body disease. *Neurology* 2007; **69**: 1460–1465.
8 Heart rate variability. Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. *Circulation* 1996; **93**: 1043–1065.
9 Varadhan R, Chaves PHM, Lipsitz LA *et al.* Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. *J Gerontol A Biol Sci Med Sci* 2009; **64**: 682–687.
10 Alter P, Grimm W, Vollrath A, Czerny F, Maisch B. Heart rate variability in patients with cardiac hypertrophy – relation to left ventricular mass and etiology. *Am Heart J* 2006; **151**: 829–836.
11 Smilde TDJ, van Veldhusen DJ, van den Berg MP. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clin Res Cardiol* 2009; **98**: 233–239.

12 Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol* 1998; **31**: 593–601.
13 Greiser KH, Kluttig A, Schumann B *et al.* Cardiovascular diseases, risk factors and short-term heart rate variability in an elderly general population: the CARLA study 2002–2006. *Eur J Epidemiol* 2009; **24**: 123–142.
14 Tsuji H, Venditti FJ Jr, Manders ES *et al.* Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994; **90**: 878–883.
15 Keith RA, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a tool for rehabilitation. *Adv Clin Rehabil* 1987; **1**: 6–18.
16 Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965; **14**: 61–65.
17 Graham I, Atar D, Borch-Johnsen K *et al.* European guidelines on cardiovascular disease prevention in clinical practice: executive summary: fourth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2007; **28**: 2375–2414.
18 Roach D, Wilson W, Ritchie D, Sheldon R. Dissection of long-range heart rate variability: controlled induction of prognostic measures by activity in the laboratory. *J Am Coll Cardiol* 2004; **43**: 2271–2277.
19 Spurr GB, Barac-Nieto M, Maksud MG. Functional assessment of nutritional status: heart rate response to submaximal work. *Am J Clin Nutr* 1979; **32**: 767–778.
20 David MDR, Martha ERR, Ernesto GR, David MDR, Martha EMDR. Sympathovagal imbalance assessed by heart rate variability correlates with percent body fat and skeletal muscle, independent of body mass index. *Cleve Clin J Med* 2011; **78**: S91a.
21 Niwa F, Kuriyama N, Nakagawa M, Imanishi J. Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. *Auton Neurosci* 2011; **165**: 195–200.
22 Boer-Martins L, Figueiredo VN, Demacq C *et al.* Relationship of autonomic imbalance and circadian disruption with obesity and type 2 diabetes in resistant hypertensive patients. *Cardiovasc Diabetol* 2011; **22**: 10–24.
23 Juha T, Korpelainen KA, Sotaniemi HV *et al.* Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. *Stroke* 1997; **28**: 2150–2154.
24 Ino-Oka E, Sekino H, Ohtaki Y, Inooka H. Effects of daily physical activity level on the degree of sympathetic tone. *Intern Med* 2009; **48**: 19–24.
25 Fortrat JO, de Germain V, Custaud MA. Holter heart rate variability: are we measuring physical activity? *Am J Cardiol* 2010; **106**: 448–449.
26 Miyamoto S, Fujita M, Sekiguchi H *et al.* Effects of posture on cardiac autonomic nervous activity in patients with congestive heart failure. *J Am Coll Cardiol* 2001; **37**: 1788–1793.
27 Dütsch M, Burger M, Dörfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. *Neurology* 2007; **69**: 2249–2255.
28 Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. *Stroke* 2004; **35**: 2094–2098.
29 Appenzeller O, Oribe E. *The Autonomic Nervous System. An Introduction to Basic and Clinical Concepts*, 5th edn. Oxford: Elsevier Science Publishers, 1997.
30 Huikuri HV, Niemelä MJ, Ojala S, Rantala A, Ikäheimo MJ, Airaksinen KE. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. *Circulation* 1994; **90**: 121–126.
31 Stein PK, Brazilay JI, Chaves PH, Domitrovich PP, Gottdiener JS. Heart rate variability and its changes over 5 years in older adults. *Age Ageing* 2009; **38**: 212–218.
32 La Rovere MT, Pinna GD, Maestri R *et al.* Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003; **107**: 565–570.
33 Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**: 256–262.
34 Nakamura T, Mizushima T, Yamamoto M, Kawazu T, Umezu Y, Tajima F. Muscle sympathetic nerve activity during isometric exercise in patients with cerebrovascular accidents. *Arch Phys Med Rehabil* 2005; **86**: 436–441.
35 Astrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac output during submaximal and maximal work. *J Appl Physiol* 1964; **19**: 268–274.
36 Koopman R, Ryall JG, Church JE, Lynch S. The role of β-adrenoceptor signaling in skeletal muscle: therapeutic implications for muscle wasting disorders. *Curr Opin Clin Nutr Metab Care* 2009; **12**: 601–606.
37 Lynch GS, Ryall JG. Role of beta-adrenoceptor signaling in skeletal muscle: implications for muscle wasting and disease. *Physiol Rev* 2008; **88**: 729–767.
38 Carter WJ, Dang AQ, Faas FH, Lynch ME. Effects of clenbuterol on skeletal muscle mass, body composition, and recovery from surgical stress in senescent rats. *Metabolism* 1991; **40**: 855–860.
39 Carter WJ, Lynch ME. Effect of clenbuterol on recovery of muscle mass and carcass protein content following dietary protein depletion in young and old rats. *J Gerontol* 1994; **49**: B162–B168.
40 Chen KD, Alway SE. Clenbuterol reduces soleus muscle fatigue during disuse in aged rats. *Muscle Nerve* 2001; **24**: 211–222.
41 Ryall JG, Plant DR, Gregorevic P, Sillence MN, Lynch GS. Beta 2-agonist administration reverses muscle wasting and improves muscle function in aged rats. *J Physiol* 2004; **555**: 175–188.
42 Ricart-Firinga C, Stevens L, Canu MH, Nemirovskaya TL, Mounier Y. Effects of beta(2)-agonist clenbuterol on biochemical and contractile properties of unloaded soleus fibers of rat. *Am J Physiol Cell Physiol* 2000; **278**: C582–C588.
43 Stevens L, Firinga C, Gohlsch B, Bastide B, Mounier Y, Pette D. Effects of unweighting and clenbuterol on myosin light and heavy chains in fast and slow muscles of rat. *Am J Physiol Cell Physiol* 2000; **279**: C1558–C1563.
44 Ryall JG, Scherzer JD, Lynch GS *et al.* Attenuation of age-related muscle wasting and weakness in rats after formoterol treatment: therapeutic implications for sarcopenia. *J Gerontol* 2007; **62A**: 813–823.
45 Peters R, Beckett N, Burch L *et al.* The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age Ageing* 2010; **39**: 609–616.
46 Lucini D, Mela GS, Malliani A, Pagani M. Impairment in cardiac autonomic regulation preceding arterial hypertension in humans: insights from spectral analysis of beat-by-beat cardiovascular variability. *Circulation* 2002; **106**: 2673–2679.

47 Burns J, Sivananthan MU, Ball SG, Mackintosh AF, Mary DA, Greenwood JP. Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. *Circulation* 2007; **115**: 1999–2005.
48 Stessman J, Rozenberg RH, Cohen A, Mor EE, Jacob JM. Physical activity, function, and longevity among the very old. *Arch Intern Med* 2009; **169**: 1476–1483.
49 Rantanen T, Voipato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc* 2003; **51**: 636–641.
50 Ling CHY, Taekema D, de Craen AJM, Gussekloo J, Westendorp RGJ, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. *CMAJ* 2010; **182**: 429–435.

ORIGINAL ARTICLE

JBMR®

# Pleiotropic Effects of Obesity on Fracture Risk: The Study of Women's Health Across the Nation

Shinya Ishii,[1] Jane A Cauley,[2] Gail A Greendale,[3] Carrie Nielsen,[4] Carrie Karvonen-Gutierrez,[5] Kristine Ruppert,[2] and Arun S Karlamangla[3]

[1]Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo, Japan
[2]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
[3]Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[4]School of Medicine, Oregon Health and Science University, CR113, Portland, OR, USA
[5]School of Public Health, University of Michigan, Ann Arbor, MI, USA

**ABSTRACT**

Some aspects of an obese body habitus may protect against fracture risk (higher bone mineral density [BMD] and greater tissue padding), while others may augment that risk (greater impact forces during a fall). To examine these competing pathways, we analyzed data from a multisite, multiethnic cohort of 1924 women, premenopausal or early perimenopausal at baseline. Obesity was defined as baseline body mass index (BMI) $> 30\,kg/m^2$. Composite indices of femoral neck strength relative to fall impact forces were constructed from DXA-derived bone size, BMD and body size. Incident fractures were ascertained annually during a median follow-up of 9 years. In multivariable linear regression adjusted for covariates, higher BMI was associated with higher BMD but with lower composite strength indices, suggesting that although BMD increases with greater skeletal loading, the increase is not sufficient to compensate for the increase in fall impact forces. During the follow-up, 201 women had fractures. In Cox proportional hazard analyses, obesity was associated with increased fracture hazard adjusted for BMD, consistent with greater fall impact forces in obese individuals. Adjusted for composite indices of femoral neck strength relative to fall impact forces, obesity was associated with decreased fracture hazard, consistent with a protective effect of soft tissue padding. Further adjustment for hip circumference, a surrogate marker of soft tissue padding, attenuated the obesity–fracture association. Our findings support that there are at least three major mechanisms by which obesity influences fracture risk: increased BMD in response to greater skeletal loading, increased impact forces, and greater absorption of impact forces by soft tissue padding. © 2014 American Society for Bone and Mineral Research.

**KEY WORDS:** OBESITY; OSTEOPOROSIS; FRACTURE RISK; STRENGTH RELATIVE TO LOAD; FALL IMPACT FORCES; SOFT TISSUE PADDING

## Introduction

Obesity has long been thought to protect against osteoporosis [1] and fragility fractures,[2] primarily because greater skeletal loading in obese individuals leads to increased bone mineral density (BMD)[2,3] and more favorable bone geometry.[4,5] However, impact forces in a fall are also greater in obese individuals because body weight is greater. Thus, for obesity to reduce fracture risk, the increase in BMD stimulated by greater skeletal loading has to compensate for greater impact forces. Unfortunately, both chronic inflammation and type 2 diabetes are also more prevalent in obese individuals, and both have deleterious influences on fracture risk;[6–9] therefore the BMD advantage from greater skeletal loading may not be sufficient to reduce one's fracture risk.

In fact, multiple recent studies report that fractures are no less common in obese individuals than in the non-obese,[10,11] and that fracture risk in some body sites (eg, extremities) is actually increased with obesity,[11–15] challenging the conventional assumption that obesity protects against fractures. There does, however, appear to be some protection conferred by obesity against fractures of the hip and pelvis in these studies.[12–15] Greater absorption of impact forces by soft tissue padding around the hip may underlie this relative reduction in hip and pelvic fracture risk in obese women;[4,11,12,14] however, the role of soft tissue padding in obesity–fracture associations has not been empirically examined in longitudinal studies.

To disentangle these disparate effects of obesity and fracture risk, we tested a series of hypotheses aimed at isolating different components in the obesity–fracture relationship. We hypothesized that:

1. Obesity would be associated with increased BMD, reflecting the increased bone mass stimulated by greater skeletal loading.

Received in original form March 17, 2014; revised form June 1, 2014; accepted June 12, 2014. Accepted manuscript online July 1, 2014.
Address correspondence to: Shinya Ishii, MD, MS, Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655 Japan. E-mail: ishiis-tky@umin.ac.jp; Sishii76@gmail.com
Journal of Bone and Mineral Research, Vol. 29, No. 12, December 2014, pp 2561–2570
DOI: 10.1002/jbmr.2303

2. Obesity would be associated with reduced bone strength relative to load (ie, that the BMD benefit of obesity would be insufficient to compensate for greater fall impact forces).
3. Adjusted for BMD (thus, removing the effects of body weight on BMD), obesity would be associated with increased fracture risk, reflecting greater fall impact forces (ie, we hypothesized that, of the remaining pathways, the influence of body weight on fall impact forces would dominate).
4. Adjusted for bone strength relative to load (thus, removing the effects of body weight on both BMD and fall impact forces), obesity would be associated with decreased fracture risk, reflecting the protective role of soft tissue padding (ie, we hypothesized that, of the remaining pathways, the protection provided by soft tissue padding would dominate).

We used data from the Hip Strength Across the Menopause Transition study to test these hypotheses.

## Materials and Methods

### Study design and population

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic longitudinal study to characterize the biological and psychosocial changes that occur during the menopausal transition. Between 1995 and 1997, a screening survey to assess study eligibility was conducted in women using either community-based or population-based sampling frames at each of seven participating clinical sites.[16] Briefly, cohort entry criteria were as follows: age 42 to 53 years, with intact uterus and at least one ovary, not using sex steroid hormones at enrollment, had at least one menstrual period in the 3 months prior to screening, and self-identified as either white, African American, Hispanic, Chinese, or Japanese. Each site recruited at least 450 eligible women into the cohort in 1996 and 1997, resulting in an inception cohort of 3302 women.[17,18]

Five sites (Boston, Detroit, Pittsburgh, Los Angeles, and Oakland) collected DXA scans of the hip and lumbar spine in all but 46 participants who weighed more than 136 kg (the scanner weight limit); they constituted the SWAN bone cohort. All five sites enrolled whites, and each site also enrolled women belonging to one prespecified minority ethnic group: African American in Boston, Detroit, and Pittsburgh and Japanese and Chinese in Los Angeles and Oakland, respectively. The Hip Strength Across the Menopause Transition study, the focus of this report, 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 (2006–2007). At baseline, 36 women did not get either bone size or body size measurements, leaving 1924 women in the analytic sample (963 white, 503 African American, 238 Japanese, and 220 Chinese). All protocols were approved by Institutional Review Boards at each site and all participants gave written informed consent.

### Assessment of BMD and bone strength relative to load

Using the OsteoDyne Hip Positioner System (Osteodyne Inc.), DXA scans of the posterior–anterior lumbar spine and total hip were acquired at the baseline visit. Hologic QDR 4500 models were used in Boston, Detroit, and Los Angeles, and QDR 2000 scanners were used in Pittsburgh and Oakland (Hologic Inc., Waltham, MA, USA). A standard quality-control program, conducted in collaboration with Synarc, Inc. (Newark, CA, USA), 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 5% random sample of scans. The 2D-projected (areal) BMD in the femoral neck and lumbar spine were recorded.

As markers of relative bone strength, we employed composite indices of femoral neck strength relative to load that integrate BMD, bone size, and (in light of the "supply and demand balance") body size.[19] They have been shown to predict fracture risk in white women[19] and in women from a multi-ethnic cohort,[20] and unlike BMD, they do not require race/ethnicity information to do so.[20] Also unlike BMD, differences in the composite strength indices between diabetics and nondiabetics are consistent with known differences in fracture risks between these groups.[7] In addition, unlike BMD, the composite strength indices are inversely associated with serum C-reactive protein (CRP) levels, a marker of chronic inflammation, and partially explain the increased fracture risk associated with inflammation.[6]

Two bone-size measurements were made on archived baseline hip scans using pixel dimensions provided by the manufacturer: femoral neck axis length (FNAL) and femoral neck width (FNW) (Fig. 1). The composite indices of femoral neck strength relative to load were computed using height, weight, FNAL, FNW, and femoral neck BMD (Fig. 1).[19] Compression strength index (CSI) reflects the ability of the femoral neck to withstand axial compressive loads proportional to body weight, bending strength index (BSI) reflects its ability to withstand bending forces proportional to body weight, and impact strength index (ISI) reflects its ability to absorb the energy of impact in a fall from standing height (which is proportional to the product of body height and weight).[19] To examine reproducibility of the composite strength indices, 20 women were scanned twice after repositioning; the intraclass correlation coefficient for each index was greater than 0.98.

### Incident fracture ascertainment and classification

During each of nine annual follow-up visits, fractures since the previous visit were self-reported using a standardized interviewer-administered questionnaire. In all years, the number of fractures, body site(s), and how fractures occurred were recorded. SWAN initiated collection of the date of fracture at follow-up visit 6. Because dates of fractures were not collected in the first six follow-ups, they were imputed using the midpoint between the participant's index and previous visits. Fractures reported at visit 6 and later were confirmed by reviewing medical records. Medical records were available for 85% of fractures and of these, only four fractures (3.8%) could not be confirmed. We excluded from all analyses factures not typically associated with osteoporosis, in particular fractures of the face, skull, fingers, and toes.[21,22] We created two categories of fractures: all fractures and minimum trauma fractures. Minimum trauma fractures excluded those that occurred as a result of a fall from a height greater than 6 inches, in a motor vehicle accident, while moving fast (eg, bicycling or skating), while playing sports, or from impact with heavy or fast-moving projectiles.

### Measurement of obesity

At the baseline and each of nine follow-up visits, height and weight were measured using a fixed stadiometer and a digital scale with the participants wearing light clothing and no shoes. The maximum hip circumference was measured over

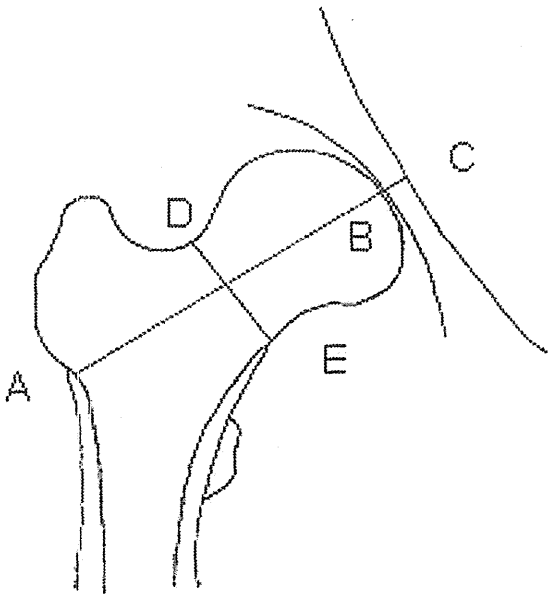


**Fig. 1.** Femoral neck size measurements and formulae to compute composite femoral neck strength indices. AB is the femoral neck axis length (FNAL), the distance from the base of the greater trochanter to the apex of the femoral head, and DE is the femoral neck width (FNW), the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis. C is where the femoral neck axis meets the inner pelvic rim. Composite femoral neck strength indices were computed using the following formulae, where BMD refers to the areal (projected 2D) bone mineral density in the femoral neck obtained from DXA:

$$\text{Compression Strength Index (CSI)} = \frac{\text{BMD}^{*}\text{FNW}}{\text{Weight}}$$

$$\text{Bending Strength Index (BSI)} = \frac{\text{BMD}^{*}\text{FNW}^{2}}{\text{FNAL}^{*}\text{Weight}}$$

$$\text{Impact Strength Index (ISI)} = \frac{\text{BMD}^{*}\text{FNW}^{*}\text{FNAL}}{\text{Height}^{*}\text{Weight}}$$

All three indices were recorded in units of g/kg-m. With BMD measured in g/cm$^2$, FNW and FNAL in cm, weight in kg, and height in meters, CSI and BSI were scaled by 100 to get values in units of g/kg-m.

undergarments (if a participant refused, over light clothing) using a measuring tape with the participants standing with their feet together. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m$^2$). Previous studies suggest nonlinear relationships between BMI and fracture risk. Therefore, participants were classified into four mutually exclusive BMI categories: low weight (BMI $<$ 22 kg/m$^2$), normal weight (22 kg/m$^2$ $\leq$ BMI $<$ 25 kg/m$^2$), overweight (25 kg/m$^2$ $\leq$ BMI $<$ 30 kg/m$^2$), and obese (30 kg/m$^2$ $\leq$ BMI). Only 39 women (2.0%) had BMI $<$ 18.5 kg/m$^2$ and therefore women with BMI $<$ 22 kg/m$^2$, which accounted for 22.5% of the analytic sample, were categorized as low weight.

## Other measurements

Participants provided the following information at baseline: age (years), race/ethnicity, menopause transition stage (premenopause or early perimenopause: no changes versus some changes in regularity of menses but with no gaps of $\geq$ 3 months), physical activity level (summary score combining intensity with frequency of active living, home, and recreational physical activity from modified Baecke interview[23]), prescription medications used, vitamin D and calcium supplement use, alcohol consumption (abstainer; infrequent: not abstainer, but $\leq$ 1 drink per week; light to moderate: $>$ 1 drink per week, but $\leq$ 1 per day; and heavy: $>$ 1 drink per day), smoking history, and comorbidities. Women who reported use of diabetes medications or had fasting serum glucose $\geq$126 mg/dL were classified as diabetic. Serum glucose was measured from blood drawn after an overnight fast, using a hexokinase-coupled reaction (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN, USA). Serum CRP level was measured at Medical Research Laboratories (Highland Heights, KY, USA), using an ultrasensitive rate immunonephelometric method with a lower limit of detection of 0.3 mg/L (BN100; Dade-Behring, Marburg, Germany). The CRP assay within-run coefficient of variation (CV) at CRP concentrations of 0.5 and 22.0 mg/L were 10%–12% and 5%–7%, respectively. During each of the follow-up visits, information on use of medications was collected using interviewer-administered questionnaires.

## Statistical analysis

The first set of analyses was designed to examine the effect of obesity on BMD and bone strength relative to load, and examined cross-sectional associations at the baseline SWAN visit. We first compared the means of the five bone strength estimates (BMD in the lumbar spine and femoral neck, and three composite indices of femoral neck strength relative to load) across BMI categories. Although we had expected to see a J-curve relationship between BMI and bone strength or fracture hazard, the preliminary analysis found a graded relationship between BMI categories and each of the bone strength estimates and fracture hazard, and we decided to set the low weight group as the reference group. The linear relationships between BMI and bone strength estimates were also tested by entering BMI into the models as a continuous variable rather than a categorical variable.

Multiple linear regression was used to adjust for the following potential confounders, which were also measured at baseline: age (continuous); race/ethnicity; menopause transition stage (premenopause versus early perimenopause); smoking status (never, past, current); alcohol use categories (abstainer, infrequent, light to moderate, heavy); level of physical activity (above median versus below median); current use (yes versus no) of medications from the following four classes (one indicator variable for each): supplementary vitamin D, supplementary calcium, other bone-active medications (oral steroids, chemotherapy for breast cancer, aromatase inhibitors, antiepileptics), and central nervous system active medications (tranquilizers, antidepressants, sedatives, sleeping pills); ever/previous use (yes versus no) of oral steroids; ever/previous use of sex steroids (oral estrogen/progesterone, estrogen patches, birth control pills); history of prior fracture as an adult (after age 20 years); and study site. Use of osteoporosis medications (bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone, or vitamin D in pharmacological doses) at baseline was reported by only one participant, and therefore the osteoporosis medications variable was not included in the models. Dunnett's method was used to adjust for multiple comparisons between the low weight (reference category) and the three higher BMI categories.

To statistically eliminate the (potentially negative) effects of chronic inflammation and diabetes from the association between BMI and bone strength estimates, we added diabetes status (yes/no) and serum CRP level (which was log-transformed to minimize its skew) to the base models, in a second step.

The second set of analyses examined obesity associations with incidence of fracture over 9 years, and employed Cox proportional hazard regression with time to first fracture as the dependent variable, and baseline BMI as primary predictor. The models were initially adjusted for the same set of baseline covariates as in the cross-sectional base model plus use in at least two consecutive visits during follow up of medications from the following four classes (using one yes/no indicator variable for each class): sex steroid hormones; osteoporosis medications; oral steroids; and other bone-active medications (chemotherapy, aromatase inhibitors, antiepileptics) as time-invariant covariates. This initial model (the longitudinal base model) estimated the overall effect of obesity on fracture risk. In subsequent models, we added select covariates representing one or more hypothesized obesity–fracture pathways in order to statistically eliminate the effects of the hypothesized pathway(-s), and estimate the obesity–fracture association independent of the selected pathway(s). We first added BMD to the model to control for the skeletal loading effect of body weight on BMD. Next, we separately added each composite index of femoral neck strength relative to load to the longitudinal base model to control for the effects of body weight on both bone mass and fall impact forces. We then further adjusted for log(CRP) and diabetes to remove any residual effects of diabetes and inflammation (which are more prevalent in obese individuals), and thus better isolate the protective effect of soft tissue padding on fracture risk. In the final model, we added a surrogate marker of soft tissue padding around the hip, derived from hip circumference to test if it explained away any remaining protective effect of obesity on fracture risk. The surrogate hip soft tissue measure was created as the residual from race/ethnicity-specific linear regressions of hip circumference on body height.

We conducted all the time-to-event analyses for each of two event types: all fractures and minimum trauma fractures. For analyses of time to first minimum-trauma fractures, follow-up time was censored at the time of the first trauma-associated fracture.[24]

A total of 96 (5.0%) women had one or more covariates missing and the missing values were imputed by single imputation using the expectation maximization (EM) algorithm.[25] All analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Two-sided $p < 0.05$ was considered statistically significant.

## Results

Participants were classified into four BMI categories: 432 (22.5%) were categorized as low weight (BMI $< 22\ kg/m^2$), 455 (23.6%) as normal weight ($22\ kg/m^2 \leq$ BMI $< 25\ kg/m^2$), 469 (24.4%) as overweight ($25 kg/m^2 \leq$ BMI $< 30\ kg/m^2$), and 568 (29.5%) as obese ($30\ kg/m^2 \leq$ BMI). Distributions of characteristics across BMI categories are shown in Table 1. African American women and women in early perimenopause were more likely to be in higher BMI categories. Diabetes, history of previous fracture, less healthier habits (current smoking and less physically active), and use of central nervous system (CNS)-active medications were also more prevalent in higher BMI categories, whereas Chinese and Japanese women and use of supplementary vitamin D and calcium were more common in lower BMI categories.

### Cross-sectional associations between BMI and estimates of bone strength

Multivariable-adjusted means of femoral neck BMD and lumbar spine BMD increased significantly with increasing BMI categories (Table 2, base model). In contrast, the adjusted means of all three composite indices of femoral neck strength relative to load decreased significantly with increasing BMI (all $p < 0.001$). Consistent with the graded increase in BMD and graded decrease in composite strength indices with increasing BMI categories, BMI as a continuous predictor was also linearly and positively associated with BMD, and linearly and negatively associated with the composite strength indices. Adjusting for diabetes and log(CRP) only slightly diminished the magnitude of the associations between BMI and the composite indices of strength relative to load (Table 2). Adjusting for diabetes and log(CRP) had virtually no impact on the associations between BMI and either lumbar spine BMD or femoral neck BMD.

### Association between baseline BMI and incident fracture

After median follow-up of 9.0 (interquartile range, 8.9–9.1) years, 201 women (10.5%) had at least one fracture, at a rate of 12.6 per 1000 person-years. Foot (non-toe) and ankle were the most common locations for first incident fracture. In Cox proportional hazard regression, adjusted for age, race/ethnicity, menopause transition stage, smoking status, alcohol use, level of physical activity, use of medications at baseline and during follow-up, history of prior fracture as an adult, and study site, fracture hazard was not significantly associated with BMI (Table 3, base model). After additional adjustment for femoral neck BMD, obesity was significantly associated with increased fracture hazard: relative increment in fracture hazard in obese relative to low weight women: 89% (95% confidence intervals (CI), 14% to 214%) (Table 3, model 2a). The relative increment in fracture hazard in obese women compared to normal weight women was also statistically significant: 78% (95% CI, 13% to 181%, $p = 0.01$). In stark contrast, obesity was significantly associated with decreased fracture hazard when adjusted instead for any of the composite indices of femoral neck strength relative to load: relative decrement in fracture hazard in obese relative to low weight women was 57% (95% CI, 24% to 76%) after adjusting for CSI, 41% (95% CI, 1% to 65%) after adjusting for BSI, and 53% (95% CI, 16% to 74%) after adjusting for ISI (Table 3, model 3). The relative decrement in fracture hazard in obese women relative to normal weight women after adjusting for CSI was 39% ($p = 0.053$). Addition of diabetes and log(CRP) to the model with CSI minimally affected the associations between BMI and fracture hazard (Table 3, model 4). Further adjustment for hip soft tissue attenuated the associations between BMI and fracture hazard and made them statistically nonsignificant (Table 3, model 5). Similar results were observed when diabetes, log(CRP), and hip soft tissue were added to Models 3b and 3c (the models with BSI and ISI)—data not shown.

Consistent with the graded associations between BMI categories and fracture hazard in models 2 through 4 (Table 3), BMI as a continuous predictor was linearly and positively associated with fracture hazard after adjusting for femoral neck or lumbar spine BMD (Table 3, models 2a and 2b), but linearly and negatively associated with fracture hazard after adjusting for composite

**Table 1.** Participant Characteristics at the Baseline Visit in the Complete Study Sample and by Body Mass Index Categories[a]

| Characteristics | All ($n = 1924$) | Low weight[b] ($n = 432$) | Normal[b] ($n = 455$) | Overweight[b] ($n = 469$) | Obese[b] ($n = 568$) | $p$ for trend[c] |
|---|---|---|---|---|---|---|
| Age (years) | 45.9 (2.7) | 45.7 (2.7) | 45.9 (2.7) | 46.1 (2.7) | 45.8 (2.7) | 0.47 |
| Height (cm) | 162.3 (6.5) | 161.0 (6.8) | 161.8 (6.5) | 163.2 (6.4) | 162.8 (6.2) | <0.001 |
| Weight (kg) | 72.6 (19.3) | 52.7 (5.4) | 61.6 (5.5) | 72.9 (6.9) | 96.3 (14.6) | <0.001 |
| BMI (kg/m$^2$) | 27.5 (6.9) | 20.3 (1.3) | 23.5 (0.9) | 27.3 (1.4) | 36.3 (5.1) | <0.001 |
| Hip circumference (cm) | 105.3 (13.9) | 91.2 (4.3) | 97.7 (4.5) | 105.5 (5.4) | 122.0 (11.3) | <.0001 |
| Waist circumference (cm) | 84.6 (15.2) | 68.9 (4.0) | 76.0 (4.4) | 85.3 (6.7) | 103.1 (11.3) | <0.001 |
| Race/ethnicity, $n$ (%) | | | | | | <0.001 |
| White | 963 (50.1) | 185 (42.8) | 236 (51.9) | 248 (52.9) | 294 (51.8) | |
| African American | 503 (26.1) | 38 (8.8) | 69 (15.2) | 141 (30.1) | 255 (44.9) | |
| Chinese | 220 (11.4) | 100 (23.2) | 72 (15.8) | 39 (8.3) | 9 (1.6) | |
| Japanese | 238 (12.4) | 109 (25.2) | 78 (17.1) | 41 (8.7) | 10 (1.8) | |
| Menopause transition stage, $n$ (%)[d] | | | | | | 0.009 |
| Premenopausal | 1087 (56.5) | 260 (60.2) | 266 (58.5) | 264 (56.3) | 297 (52.3) | |
| Early perimenopausal | 837 (43.5) | 172 (39.8) | 189 (41.5) | 205 (43.7) | 271 (47.7) | |
| Smoking Status, $n$ (%) | | | | | | <0.001 |
| Never smoked | 1142 (59.8) | 280 (65.1) | 287 (63.2) | 266 (57.2) | 309 (55.0) | |
| Ex-smoker | 486 (25.4) | 92 (21.4) | 112 (24.7) | 128 (27.5) | 154 (27.4) | |
| Current smoker | 283 (14.8) | 58 (13.5) | 55 (12.1) | 71 (15.3) | 99 (17.6) | |
| Alcohol consumption, $n$ (%)[e] | | | | | | <0.001 |
| Abstainer | 992 (51.6) | 199 (46.3) | 218 (48.0) | 235 (50.1) | 340 (59.9) | |
| Infrequent | 179 (9.3) | 47 (10.9) | 37 (8.2) | 41 (8.7) | 54 (9.5) | |
| Light to moderate | 489 (25.5) | 112 (26.1) | 125 (27.5) | 121 (25.8) | 131 (23.1) | |
| Heavy | 261 (13.6) | 72 (16.7) | 74 (16.3) | 72 (15.4) | 43 (7.6) | |
| Physical activity level, $n$ (%) | | | | | | <0.001 |
| Above median | 945 (50.6) | 247 (59.1) | 257 (57.8) | 243 (53.3) | 198 (36.2) | |
| Below median | 921 (49.4) | 171 (40.9) | 188 (42.3) | 213 (46.7) | 349 (63.8) | |
| History of prior fracture as adult, $n$ (%) | 353 (18.4) | 57 (13.2) | 72 (15.8) | 101 (21.5) | 123 (21.7) | <0.001 |
| Current use of medications, $n$ (%) | | | | | | |
| Supplementary vitamin D | 742 (38.6) | 177 (41.2) | 175 (38.6) | 182 (38.8) | 208 (36.6) | 0.17 |
| Supplementary calcium | 863 (44.9) | 218 (50.7) | 212 (46.7) | 208 (44.4) | 225 (39.6) | <0.001 |
| CNS active medications[f] | 199 (10.3) | 39 (9.0) | 37 (8.1) | 47 (10.0) | 76 (13.4) | 0.01 |
| Other bone-active medications[g] | 44 (2.3) | 8 (1.9) | 7 (1.5) | 13 (2.8) | 16 (2.8) | 0.17 |
| Previous use of medications, $n$ (%) | | | | | | |
| Sex steroid hormones | 1419 (73.8) | 287 (66.4) | 330 (72.5) | 357 (76.1) | 445 (78.4) | <0.001 |
| Oral steroids | 92 (4.8) | 13 (3.0) | 20 (4.4) | 21 (4.5) | 38 (6.7) | 0.008 |
| Diabetes mellitus, $n$ (%)[h] | 88 (4.6) | 3 (0.7) | 7 (1.5) | 10 (2.1) | 68 (12.0) | <0.001 |
| FNAL (cm) | 8.97 (0.51) | 8.98 (0.54) | 8.98 (0.51) | 9.01 (0.51) | 8.91 (0.48) | 0.09 |
| FNW (cm) | 2.75 (0.20) | 2.73 (0.20) | 2.73 (0.20) | 2.75 (0.20) | 2.78 (0.20) | <0.001 |
| Lumbar spine BMD (g/cm$^2$) | 1.07 (0.13) | 1.00 (0.11) | 1.04 (0.12) | 1.09 (0.13) | 1.13 (0.13) | <0.001 |
| Femoral neck BMD (g/cm$^2$) | 0.84 (0.13) | 0.75 (0.10) | 0.80 (0.10) | 0.85 (0.11) | 0.95 (0.13) | <0.001 |
| CSI (g/kg-m) | 3.31 (0.64) | 3.90 (0.55) | 3.54 (0.47) | 3.20 (0.43) | 2.76 (0.45) | <0.001 |
| BSI (g/kg-m) | 1.02 (0.22) | 1.19 (0.21) | 1.08 (0.19) | 0.98 (0.16) | 0.87 (0.16) | <0.001 |
| ISI (g/kg-m) | 0.18 (0.04) | 0.22 (0.03) | 0.20 (0.03) | 0.18 (0.02) | 0.15 (0.03) | <0.001 |

Abbreviations: BMI, body mass index; CNS, central nervous system; FNAL, femoral neck axis length; FNW, femoral neck width; CSI, compression strength index; BSI, bending strength index; ISI, impact strength index.

[a]Mean and standard deviation shown for continuous variables and number of participants and percentage shown for categorical variables.

[b]BMI categories: low weight: BMI $< 22$, normal: $22 \leq$ BMI $< 25$, overweight: $25 \leq$ BMI $< 30$, and obese: $30 \leq$ BMI.

[c]$p$ value for trend across increasing BMI categories was calculated using the Jonckheere-Terpstra test.

[d]Women were classified as premenopausal if they had experienced at least one menstrual period in the last 3 months with no change in the regularity of their menstrual bleeding during the last year and early perimenopausal if they had experienced at least one menstrual period in the last 3 months with some change in the regularity of their menstrual bleeding during the last year.

[e]Women were classified as abstainer if they consumed no alcohol, infrequent if they consumed less than one drink per week, light to moderate if they consumed more than one drink per week but less than one drink per day, and heavy if they consumed more than one drink per day.

[f]CNS active medications include tranquilizers, antidepressants, sedatives, and sleeping pills.

[g]Other bone-active medications include oral steroids, chemotherapy for breast cancer, aromatase inhibitors, and antiepileptics.

[h]Women who reported use of diabetes medications or had fasting serum glucose $\geq 126$ mg/dL were classified as diabetic.

**Table 2.** Adjusted* Means of Bone Mineral Density and Indices of Bone Strength Relative to Load as Function of Body Mass Index[a]

| | Reference (BMI < 22) | Normal (22 ≤ BMI < 25) | | Overweight (25 ≤ BMI < 30) | | Obese (30 ≤ BMI) | | BMI as continuous predictor | |
|---|---|---|---|---|---|---|---|---|---|
| | Adjusted mean | Adjusted mean difference from the reference group | *p* | Adjusted mean difference from the reference group | *p* | Adjusted mean difference from the reference group | *p* | Adjusted increment in mean per unit BMI increment (kg/m$^2$) | *p* |
| Femoral neck BMD (g/cm$^2$) | | | | | | | | | |
| Base model[b] | 0.76 | 0.04 (0.03, 0.06) | <0.001 | 0.08 (0.06, 0.09) | <0.001 | 0.17 (0.15, 0.18) | <0.001 | 0.0078 (0.0069, 0.0087) | <0.001 |
| + DM and CRP[c] | 0.78 | 0.04 (0.03, 0.06) | <0.001 | 0.08 (0.06, 0.09) | <0.001 | 0.16 (0.14, 0.19) | <0.001 | 0.0080 (0.0069, 0.0091) | <0.001 |
| Lumbar spine BMD (g/cm$^2$) | | | | | | | | | |
| Base model | 1.01 | 0.04 (0.02, 0.06) | <0.001 | 0.08 (0.06, 0.10) | <0.001 | 0.13 (0.11, 0.15) | <0.001 | 0.0097 (0.0089, 0.0105) | <0.001 |
| + DM and CRP | 1.03 | 0.04 (0.02, 0.06) | <0.001 | 0.08 (0.06, 0.10) | <0.001 | 0.13 (0.11, 0.16) | <0.001 | 0.0099 (0.0090, 0.0108) | <0.001 |
| CSI (g/kg-m) | | | | | | | | | |
| Base model | 3.88 | −0.33 (−0.41, −0.26) | <0.001 | −0.66 (−0.73, −0.58) | <0.001 | −1.07 (−1.14, −0.98) | <0.001 | −0.062 (−0.066, −0.059) | <0.001 |
| + DM and CRP | 3.81 | −0.30 (−0.37, −0.23) | <0.001 | −0.60 (−0.68, −0.53) | <0.001 | −0.95 (−1.04, −0.86) | <0.001 | −0.059 (−0.063, −0.055) | <0.001 |
| BSI (g/kg-m) | | | | | | | | | |
| Base model | 1.17 | −0.09 (−0.12, −0.07) | <0.001 | −0.18 (−0.21, −0.15) | <0.001 | −0.28 (−0.31, 0.25) | <0.001 | −0.016 (−0.017, −0.015) | <0.001 |
| + DM and CRP | 1.15 | −0.09 (−0.11, −0.06) | <0.001 | −0.16 (−0.19, −0.13) | <0.001 | −0.24 (−0.28, −0.21) | <0.001 | −0.015 (−0.017, −0.014) | <0.001 |
| ISI (g/kg-m) | | | | | | | | | |
| Base model | 0.22 | −0.020 (−0.024, −0.016) | <0.001 | −0.039 (−0.043, −0.035) | <0.001 | −0.063 (−0.068, −0.059) | <0.001 | −0.0037 (−0.0039, −0.0035) | <0.001 |
| + DM and CRP | 0.21 | −0.018 (−0.022, −0.014) | <0.001 | −0.035 (−0.040, −0.031) | <0.001 | −0.055 (−0.061, −0.050) | <0.001 | −0.0034 (−0.0037, −0032) | <0.001 |

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CRP, C-reactive protein; CSI, compression strength index; BSI, bending strength index; ISI, impact strength index; BMD, bone mineral density

[a]Results of multiple linear regression analysis with BMI as categorical predictor (reference group: low weight category, BMI < 22kg/m$^2$) and as continuous predictor in separate models.

[b]Base model: Adjusts for age, menopause transition stage, race/ethnicity, study site, physical activity, smoking status and alcohol consumption, history of fracture since age 20, baseline use of medications (supplementary vitamin D, supplementary calcium, bone-active medications, central nervous system active medications, ever/previous use of oral steroids, and ever/previous use of sex steroids).

[c]DM and CRP were added in step 2.

**Table 3.** Adjusted* Associations Between Body Mass Index and Incident Fracture Before and After Controlling for Different Pathways[a]

| | Normal ($22 \leq BMI < 25$) | | Overweight ($25 \leq BMI < 30$) | | Obese ($30 \leq BMI$) | | BMI as continuous predictor | |
|---|---|---|---|---|---|---|---|---|
| | Ref: Low weight | | Ref: Low weight | | Ref: Low weight | | Per unit BMI increment ($kg/m^2$) | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Base model[b] | 0.91 (0.58, 1.41) | 0.67 | 1.02 (0.66, 1.59) | 0.93 | 1.01 (0.64, 1.59) | 0.97 | 1.01 (0.98, 1.03) | 0.58 |
| Model 2a | 1.06 (0.68, 1.67) | 0.79 | 1.32 (0.84, 2.08) | 0.22 | 1.89 (1.14, 3.14) | 0.01 | 1.05 (1.02, 1.07) | <.001 |
| Model 2b | 1.03 (0.66, 1.62) | 0.89 | 1.27 (0.81, 1.99) | 0.30 | 1.50 (0.93, 2.42) | 0.10 | 1.03 (1.005, 1.06) | 0.02 |
| Model 3a | 0.70 (0.44, 1.10) | 0.12 | 0.59 (0.36, 0.97) | 0.04 | 0.43 (0.24, 0.76) | 0.004 | 0.96 (0.93, 0.99) | 0.006 |
| Model 3b | 0.76 (0.48, 1.20) | 0.24 | 0.72 (0.45, 1.16) | 0.18 | 0.59 (0.35, 0.99) | 0.048 | 0.98 (0.95, 1.003) | 0.08 |
| Model 3c | 0.71 (0.45, 1.13) | 0.15 | 0.63 (0.38, 1.03) | 0.07 | 0.47 (0.26, 0.84) | 0.01 | 0.96 (0.93, 0.99) | 0.02 |
| Model 4 | 0.71 (0.45, 1.13) | 0.15 | 0.62 (0.37, 1.02) | 0.06 | 0.43 (0.23, 0.81) | 0.009 | 0.95 (0.92, 0.99) | 0.005 |
| Model 5 | 0.76 (0.48, 1.22) | 0.26 | 0.72 (0.42, 1.23) | 0.23 | 0.65 (0.31, 1.40) | 0.27 | 0.98 (0.91, 1.04) | 0.47 |

Abbreviations: BMI, body mass index; HR, hazard ratio, CI, confidence intervals.

[a]Results of Cox proportional hazards analysis with BMI as categorical predictor (reference group: low weight category, $BMI < 22 kg/m^2$) and as continuous predictor in separate models.

[b]Base model: age, menopause transition stage, race/ethnicity, study site, physical activity, smoking status and alcohol consumption, history of fracture since age 20, baseline use of medications (supplementary vitamin D, supplementary calcium, bone-active medications, central nervous system active medications, ever/previous use of oral steroids, and ever/previous use of sex steroids) and use of medications during the follow-up (sex steroid hormones, osteoporosis medications, oral steroids, and other bone-active medications).

Model 2a: adjusted for covariates in base model plus femoral neck BMD. Model 2b: adjusted for covariates in base model plus lumbar spine BMD. Model 3a: adjusted for covariates in base model plus compression strength index. Model 3b: adjusted for covariates in base model plus bending strength index. Model 3c: adjusted for covariates in base model plus impact strength index.

Model 4: adjusted for covariates in model 3a plus diabetes status and log (C-reactive protein). Model 5: adjusted for covariates in model 4 plus a surrogate measure of hip soft tissue.

indices of femoral neck strength relative to load (Table 3, models 3a and 3c). Similarly, the linear and negative relationship between BMI (as a continuous predictor) and fracture hazard became nonsignificant when hip soft tissue was added to the model (Table 3, model 5).

### Association between baseline BMI and incident minimum trauma fracture

After the 9-year follow-up, 82 women (4.3%) had at least one minimum trauma fracture, at a rate of 5.1 per 1000 person-years. Findings for minimum trauma fracture were similar to the ones for all fracture with respect to the direction and magnitude of the associations with BMI (Table 4). However, reflecting the smaller number of events, fewer associations reached levels of statistical significance.

## Discussion

This study was designed to test multiple hypothesized pathways by which obesity might affect fracture risk: (1) increased BMD in response to greater skeletal loading, (2) increased impact forces in a fall (load), (3) deleterious effects of chronic inflammation and diabetes (common in obesity) on bone mass, and (4) absorption of impact forces by soft tissue padding. Using data from a multi-ethnic cohort of 1924 women going through the menopause transition, we demonstrated that although higher BMI was indeed associated with higher BMD (consistent with previous studies[2,3]), it is in fact associated with lower indices of bone strength relative to load. These associations between BMI and the bone strength estimates were monotonic. These findings suggest that although obesity may increase BMD, the increase in bone strength is not commensurate with the increase in fall impact forces. Further adjustment for the detrimental effects of diabetes and inflammation did not substantially alter the associations between high BMI and low bone strength.

We also demonstrated that adjusted for BMD, obesity was associated with increased fracture hazard. Increased fracture hazard in obesity, when adjusted for BMD, has been seen in previous studies[10,26] and is consistent with the hypothesis that larger fall impact forces in obesity increase fracture risk. We also demonstrated that obesity was associated with decreased fracture hazard after adjustment for any of the three composite indices of bone strength relative to fall impact forces. Since controlling for the composite indices statistically eliminates the effects of obesity on both bone strength and fall impact forces without eliminating the effect of soft tissue padding, this is consistent with a fracture protection effect of soft tissue padding. Such a protective role is further supported by the observation that additional adjustment for a surrogate marker for hip soft tissue padding attenuated the remaining obesity–fracture association and made it statistically nonsignificant.

Taken together, these findings provide empirical evidence for the hypothesized pleiotropic effects of obesity on fracture risk. First, bone mass increases in response to the excess weight. Second, obesity increases fracture risk by increasing impact forces in a fall. The increase in bone mass in obesity is not commensurate with the increased fall impact forces. Third, the reduction in bone strength relative to load is to some degree offset by the protection conferred by increased soft tissue padding. The balance between these factors determines the overall fracture risk in an individual.

Because the magnitude of these competing effects can vary from body site to body site, the relationship between obesity and fracture will be both site-specific and person-specific. For instance, the adaptive increase in BMD due to greater skeletal loading will be more pronounced at weight-bearing sites such as the hip and spine than in the forearm and wrist. Similarly, the protection conferred by soft tissue mass will be greatest at body sites where it is most abundant, and the localization of soft tissue can vary from person to person. For instance, gynecoid obesity, where most fat accumulation is around the hip, should provide

**Table 4.** Adjusted[a] Associations Between Body Mass Index and Incident Minimum Trauma Fracture Before and After Controlling for Different Pathways[a]

| | Obese (30 ≤ BMI) | | BMI as continuous predictor | |
|---|---|---|---|---|
| | Ref: Low weight | | Per unit BMI increment (kg/m$^2$) | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Base model[b] | 1.06 (0.49, 2.28) | 0.88 | 1.02 (0.98, 1.05) | 0.35 |
| Model 2a | 1.78 (0.77, 4.13) | 0.18 | 1.05 (1.01, 1.09) | 0.01 |
| Model 2b | 1.58 (0.71, 3.51) | 0.26 | 1.04 (1.004, 1.08) | 0.03 |
| Model 3a | 0.33 (0.13, 0.87) | 0.02 | 0.96 (0.92, 1.007) | 0.10 |
| Model 3b | 0.47 (0.20, 1.10) | 0.08 | 0.98 (0.94, 1.02) | 0.23 |
| Model 3c | 0.39 (0.15, 1.005) | 0.051 | 0.97 (0.93, 1.02) | 0.22 |
| Model 4 | 0.29 (0.10, 0.80) | 0.02 | 0.95 (0.90, 1.001) | 0.053 |
| Model 5 | 0.30 (0.09, 1.03) | 0.055 | 0.95 (0.86, 1.05) | 0.31 |

Abbreviations: BMI, body mass index; HR, hazard ratio, CI, confidence intervals.

[a]Results of Cox proportional hazards analysis with BMI as categorical predictor (reference group: low weight category, BMI < 22kg/m$^2$) and as continuous predictor in separate models.

[b]Base model: age, menopause transition stage, race/ethnicity, study site, physical activity, smoking status and alcohol consumption, history of fracture since age 20, baseline use of medications (supplementary vitamin D, supplementary calcium, bone-active medications, central nervous system active medications, ever/previous use of oral steroids, and ever/previous use of sex steroids) and use of medications during the follow-up (sex steroid hormones, osteoporosis medications, oral steroids, and other bone-active medications). Model 2a: adjusted for covariates in base model plus femoral neck BMD. Model 2b: adjusted for covariates in base model plus lumbar spine BMD. Model 3a: adjusted for covariates in base model plus compression strength index. Model 3b: adjusted for covariates in base model plus bending strength index. Model 3c: adjusted for covariates in base model plus impact strength index. Model 4: adjusted for covariates in model 3a plus diabetes status and log(C-reactive protein). Model 5: adjusted for covariates in model 4 plus a surrogate measure of hip soft tissue.

protection against hip fractures, but not necessarily protect against fractures at other appendicular sites. This is consistent with previous studies which found lower hip fracture risk[4,11,12,14] but higher risk of fractures elsewhere[11–15] in obese compared to non-obese women.

Previous studies have found that both inflammation and diabetes, which are more prevalent in obesity, have deleterious effects on bone strength and fracture risk[6–9] and that diabetes is also associated with increased fall risk.[27,28] The observed negative associations of obesity with both bone strength relative to load and fracture risk independent of inflammation and diabetes in this current study suggests that there are other direct mechanisms by which obesity is deleterious to bone health. Adipose tissue is considered an endocrine organ producing adipokines such as adiponectin and leptin, which have been implicated in bone metabolism.[29] Increased bone marrow fat in obesity may also have deleterious effects on bone.[30] Other possible mechanisms include osteoarthritis (which increases fall risk),[11,31] prediabetes, hyperlipidemia, hypertension, and vascular atherosclerosis (which may reduce blood and oxygen supply to bone), all of which are more prevalent in obese individuals.

It should be noted that the composite strength indices employed in this study are structural measures based on macroscopic measurements from DXA scans and body size derived from structural engineering principles. The indices ignore important microscopic features such as differences in microarchitecture, and a recent case control study did demonstrate that obesity-induced improvements in microarchitecture may also not be commensurate with the increased body weight.[32] In addition, the strength indices were derived using the simplifying assumption that the femoral neck is a simple cylinder and do not take into account other aspects of shape such as femoral neck-shaft angle, which may also be influenced by body composition[4,33] and associated with hip fracture risk.[34] These other pathways from obesity to fracture risk need further investigation.

Our study has other limitations to be noted. First, fractures were self-reported, but fractures after visit 6 were confirmed by medical records review. It is still possible that we overlooked clinically silent vertebral fractures. Also, the exact date of fracture was not recorded until the medical records review process began; thus, fractures that occurred prior to that time were assumed to occur at the midpoint between the current and prior visit. This could bias our estimates.[35] Second, we employed BMI as a measure of obesity and did not assess the role of truncal versus appendicular distribution of fat or distinguish fat mass from lean mass. We also did not differentiate between visceral and subcutaneous adipose tissues, each of which may have different biological implications.[36] Third, the composite strength indices were designed to quantify bone strength in the femoral neck, but fractures in the femoral neck were relatively rare in this cohort of middle-aged women (less than 5% of all fractures). However, just like low or high BMD in the femoral neck is a reflection of low or high bone mass more generally,[22] femoral neck strength indices also reflect bone strength elsewhere in the individual and predict fracture risk more generally.[20,37] Fourth, the incidence of fracture was low in this cohort of middle-aged women, precluding analyses by specific locations of bone fractures and limiting our power to detect residual BMI effects after adjusting for hip soft tissue. Lastly, we did not take into account the change in BMD or bone strength indices during follow-up, which may also be influenced by obesity. Further studies are warranted to assess the generalizability of our findings to other populations, such as men, older postmenopausal women, and younger premenopausal women.

In summary, this study provided empirical evidence for at least three major mechanisms by which obesity may influence fracture risk: adaptive increase in BMD, increased impact forces in a fall, and soft tissue padding to absorb impact forces. Our findings suggest that the assessment of fracture risk has to go beyond measurement of BMD to include assessment of bone strength relative to load and the extent of soft tissue over potential impact sites.

## Disclosures

All authors state that they have no conflicts of interest.

## Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the NIH Office of Research on Women's Health (ORWH) (grants U01NR004061, U01AG012505,

U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, and U01AG012495). The Hip Strength Through the Menopausal Transition Study is supported by the NIA (AG026463). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, or the NIH.

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, NJ—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.

We thank the study staff at each site and all the women who participated in SWAN.

Authors' roles Study Concept: AK, SI, GG, and JC. Data analysis: SI. Obtain funding: AK, GG, and JC. Data interpretation: SI, AK, GG, and CC. Drafting manuscript: SI. Revising manuscript content: SI, AK GG, JC, CN, CKG, and KR. Approving final version of manuscript: SI, AK GG, JC, CN, CKG, and KR. SI takes responsibility for the integrity of the data analysis.

## References

1. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. 2005;16:1330–8.
2. Looker AC, Flegal KM, Melton LJ 3rd. Impact of increased overweight on the projected prevalence of osteoporosis in older women. Osteoporos Int. 2007;18:307–13.
3. Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. J Bone Miner Res. 1993;8:567–73.
4. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. J Bone Miner Res. 2009;24:1369–79.
5. Beck TJ, Oreskovic TL, Stone KL, Ruff CB, Ensrud K, Nevitt MC, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: the study of osteoporotic fractures. J Bone Miner Res. 2001;16:1108–19.
6. Ishii S, Cauley JA, Greendale GA, Crandall CJ, Danielson ME, Ouchi Y, et al. C-reactive protein, bone strength, and 9-year fracture risk: Data from the study of women's health across the nation (SWAN). J Bone Miner Res. 2013;28:1688–98.
7. Ishii S, Cauley JA, Crandall CJ, Srikanthan P, Greendale GA, Huang MH, et al. Diabetes and femoral neck strength: findings from the Hip Strength Across the Menopausal Transition Study. J Clin Endocrinol Metab. 2012;97:190–7.
8. Cauley JA, Danielson ME, Boudreau RM, Forrest KY, Zmuda JM, Pahor M, et al. Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. J Bone Miner Res. 2007;22:1088–95.
9. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int. 2007;18:427–44.
10. Nielson CM, Marshall LM, Adams AL, LeBlanc ES, Cawthon PM, Ensrud K, et al. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). J Bone Miner Res. 2011;26:496–502.
11. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med. 2011;124:1043–50.
12. Prieto-Alhambra D, Premaor MO, Fina Aviles F, Hermosilla E, Martinez-Laguna D, Carbonell-Abella C, et al. The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. J Bone Miner Res. 2012;27:294–300.
13. Compston JE, Flahive J, Hosmer DW, Watts NB, Siris ES, Silverman S, et al. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopausal women: The global longitudinal study of osteoporosis in women (GLOW). J Bone Miner Res. 2014;29:487–93.
14. Premaor MO, Compston JE, Fina Aviles F, Pages-Castella A, Nogues X, Diez-Perez A, et al. The association between fracture site and obesity in men: A population-based cohort study. J Bone Miner Res. 2013;28:1771–7.
15. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. Osteoporos Int. 2013;24:69–76.
16. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009;54:2366–73.
17. Randolph JF Jr, Zheng H, Sowers M, Crandall C, Crawford S, Gold EB, et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. J Clin Endocrinol Metab. 2011;96:746–54.
18. Sowers M, Crawford S, Sternfeld B, Morganstein D, Gold E, Greendale G, et al. Design, survey, sampling and recruitment methods of SWAN: a multi-center, multi-ethnic, community based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus M, editors. Menopause: biology and pathobiology. San Diego: Academic Press; 2000. pp175–88.
19. Karlamangla AS, Barrett-Connor E, Young J, Greendale GA. Hip fracture risk assessment using composite indices of femoral neck strength: the Rancho Bernardo study. Osteoporos Int. 2004;15:62–70.
20. Ishii S, Greendale GA, Cauley JA, Crandall CJ, Huang MH, Danielson ME, et al. Fracture risk assessment without race/ethnicity information. J Clin Endocrinol Metab. 2012;97:3593–602.
21. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1991;115:837–42.
22. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. 2003;18:1947–54.
23. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;36:936–42.
24. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics. 1978;34:541–54.
25. Graham JW. Missing data analysis: making it work in the real world. Annu Rev Psychol. 2009;60:549–76.

26. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res. 2014;29:223–33.
27. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care. 2002;25:1749–54.
28. Wallace C, Reiber GE, LeMaster J, Smith DG, Sullivan K, Hayes S, et al. Incidence of falls, risk factors for falls, and fall-related fractures in individuals with diabetes and a prior foot ulcer. Diabetes Care. 2002;25:1983–6.
29. Biver E, Salliot C, Combescure C, Gossec L, Hardouin P, Legroux-Gerot I, et al. Influence of adipokines and ghrelin on bone mineral density and fracture risk: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96:2703–13.
30. Duque G. Bone and fat connection in aging bone. Curr Opin Rheumatol. 2008;20:429–34.
31. Griffin TM, Guilak F. Why is obesity associated with osteoarthritis? Insights from mouse models of obesity. Biorheology. 2008;45:387–98.
32. Sornay-Rendu E, Boutroy S, Vilayphiou N, Claustrat B, Chapurlat RD. In obese postmenopausal women, bone microarchitecture and strength are not commensurate to greater body weight: the Os des Femmes de Lyon (OFELY) study. J Bone Miner Res. 2013;28:1679–87.
33. Hu WW, Zhang H, Wang C, Gu JM, Yue H, Ke YH, et al. Lean mass predicts hip geometry and bone mineral density in chinese men and women and age comparisons of body composition. J Clin Densitom. 2012;15:434–42.
34. Bergot C, Bousson V, Meunier A, Laval-Jeantet M, Laredo JD. Hip fracture risk and proximal femur geometry from DXA scans. Osteoporos Int. 2002;13:542–50.
35. Law CG, Brookmeyer R. Effects of mid-point imputation on the analysis of doubly censored data. Stat Med. 1992;11:1569–78.
36. Gilsanz V, Chalfant J, Mo AO, Lee DC, Dorey FJ, Mittelman SD. Reciprocal relations of subcutaneous and visceral fat to bone structure and strength. J Clin Endocrinol Metab. 2009;94:3387–93.
37. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet. 1993;341:72–5.

Bone 73 (2015) 160–166

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

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

ARTICLE INFO

*Article history:*
Received 9 September 2014
Revised 18 November 2014
Accepted 8 December 2014
Available online 18 December 2014

Edited by Mark Cooper

*Keywords:*
Parity
Lactation
Fracture
Bone strength
Bone mineral density
Composite strength indices

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 re-accrual (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).

http://dx.doi.org/10.1016/j.bone.2014.12.013
8756-3282/

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

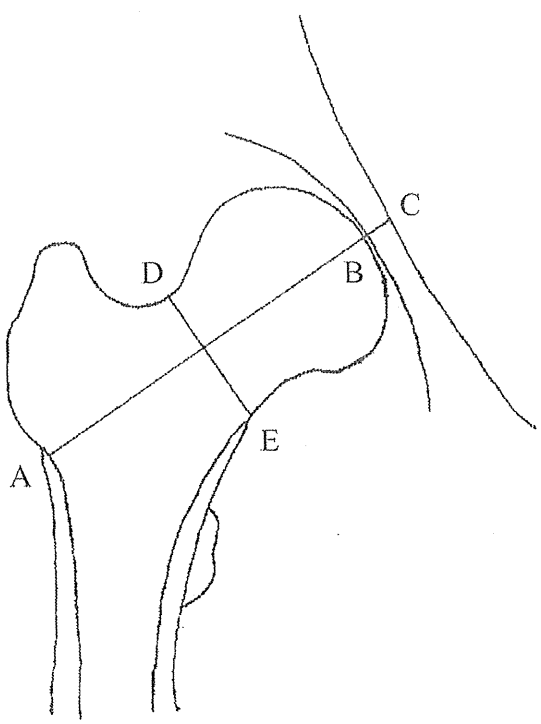


**Fig. 1.** Femoral neck size measurements. AB is the femoral neck axis length (FNAL): the distance from the base of the greater trochanter to the apex of the femoral head. DE is the femoral neck width (FNW): the smallest thickness of the femoral neck along any line perpendicular to the femoral neck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

## Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The Hip Strength Through the Menopausal Transition has grant support from the NIA (AG026463). Takahiro Mori was supported by the VA Special Fellowship Program in Advanced Geriatrics and the VA Greater Los Angeles Geriatric Research Education and Clinical Center. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, VA or the NIH.

*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

We thank the study staff at each site and all the women who participated in SWAN.

## 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.

## Disclosures

All authors state that they have no conflicts of interest.

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The Hip Strength Through the Menopausal Transition has grant support from the NIA (AG026463).

## References

[1] Specker BL. Bone mineral changes during pregnancy and lactation. Endocrine 2002; 17:49–53.
[2] Karlsson MK, Ahlborg HG, Karlsson C. Female reproductive history and the skeleton — a review. BJOG: Int J Obstet Gynaecol 2005;112:851–6.
[3] Møller U, vid Streym S, Mosekilde L, Rejnmark L. Changes in bone mineral density and body composition during pregnancy and postpartum. A controlled cohort studyOsteoporos Int 2012;23:1213–23.
[4] Alonso CG, Curiel M, Carranza F, Cano R, Perez A. Femoral bone mineral density, neck-shaft angle and mean femoral neck width as predictors of hip fracture in men and women. Multicenter Project for Research in Osteoporosis. Osteoporos Int 2000;11:714.
[5] Faulkner KG, Cummings SR, Black D, Palermo L, Glüer CC, Genant HK. Simple measurement of femoral geometry predicts hip fracture: the study of osteoporotic fractures. J Bone Miner Res 2009;8:1211–7.
[6] Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative — observational study. J Bone Miner Res 2009;24:1369–79.
[7] Specker B, Binkley T. High parity is associated with increased bone size and strength. Osteoporos Int 2005;16:1969–74.
[8] Wiklund P, Xu L, Wang Q, Mikkola T, Lyytikäinen A, Völgyi E, et al. Lactation is associated with greater maternal bone size and bone strength later in life. Osteoporos Int 2012;23:1939–45.
[9] Laskey M, Price R, Khoo B, Prentice A. Proximal femur structural geometry changes during and following lactation. Bone 2011;48:755–9.
[10] Gunderson EP. Childbearing and obesity in women: weight before, during, and after pregnancy. Obstet Gynecol Clin North Am 2009;36:317–32.
[11] Nehring I, Schmoll S, Beyerlein A, Hauner H, von Kries R. Gestational weight gain and long-term postpartum weight retention: a meta-analysis. Am J Clin Nutr 2011;94:1225–31.
[12] Chung M, Raman G, Chew P, Magula N, Trikalinos T, Lau J. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Technol Asses (Full Rep) 2007;153:1–186.
[13] Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham Study. J Bone Miner Res 1993;8:567–73.
[14] Ishii S, Cauley JA, Greendale GA, Nielsen C, Karvonen-Gutierrez C, Ruppert K, et al. Pleiotropic effects of obesity on fracture risk: the Study of Women's Health Across the Nation. J Bone Miner Res 2014;29(12):2561–70.
[15] Karlamangla AS, Barrett-Connor E, Young J, Greendale GA. Hip fracture risk assessment using composite indices of femoral neck strength: the Rancho Bernardo study. Osteoporos 2004;15:62–70.
[16] Ishii S, Greenda e GA, Cauley JA, Crandall CJ, Huang M-H, Danielson ME, et al. Fracture risk assessment without race/ethnicity information. J Clin Endocrinol Metab 2012;97:3593–602.
[17] Ishii S, Cauley JA, Crandall CJ, Srikanthan P, Greendale GA, Huang M-H, et al. Diabetes and femoral neck strength: findings from the Hip Strength Across the Menopausal Transition Study. J Clin Endocrinol Metab 2012;97:190–7.
[18] Ishii S, Cauley J, Greendale G, Danielson M, Nili NS, Karlamangla A. Ethnic differences in composite indices of femoral neck strength. Osteoporos Int 2012;23:1381–90.
[19] Heaney R, Abrams S, Dawson-Hughes B, Looker A, Looker A, Marcus R, et al. Peak bone mass. Osteoporos Int 2000;11:985–1009.
[20] Riis BJ, Hansen MA, Jensen AM, Overgaard K, Christiansen C. Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture: a 15-year follow-up study. Bone 1996;19:9–12.
[21] Cauley JA, Danielson ME, Greendale GA, Finkelstein JS, Chang Y-F, Lo JC, et al. Bone resorption and fracture across the menopausal transition: the Study of Women's Health Across the Nation. Menopause 2012;19:1200–7.
[22] Sowers MCS, Sternfeld B, Morganstein D, Gold E, Greendale G, Evans D, et al. Design, survey, sampling and recruitment methods of SWAN: a multi-center, multi-ethnic, community based cohort study of women and the menopausal transition. Menopause: biol pathobiol 2000:175–88 [Academic Press, San Diego].
[23] Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab 2008;93:861–8.
[24] Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36: 936–42.
[25] Mori T, Ishii S, Greendale GA, Cauley JA, Sternfeld B, Crandall CJ, et al. Physical activity as determinant of femoral neck strength relative to load in adult women: findings from the Hip Strength Across the Menopause Transition Study. Osteoporos Int 2014;25:265–72.
[26] Horton NJ, Lipsitz SR. Multiple imputation in practice: comparison of software packages for regression models with missing variables. Am Stat 2001;55:244–54.
[27] Heitjan DF, Little RJ. Multiple imputation for the fatal accident reporting system. Appl Stat 1991;13–29.
[28] Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? Ann Intern Med 1991;115:837–42.
[29] Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res 2003;18:1947–54.
[30] Lissner L, Bengtsson C, Hansson T. Bone mineral content in relation to lactation history in pre-and postmenopausal women. Calcif Tissue Int 1991;48:319–25.
[31] Kojima N, Douchi T, Kosha S, Nagata Y. Cross-sectional study of the effects of parturition and lactation on bone mineral density later in life. Maturitas 2002; 41:203–9.
[32] Dursun N, Akın S, Dursun E, Sade I, Korkusuz F. Influence of duration of total breastfeeding on bone mineral density in a Turkish population: does the priority of risk factors differ from society to society? Osteoporos Int 2006;17:651–5.
[33] Tsvetov G, Levy S, Benbassat C, Shraga-Slutzky I, Hirsch D. Influence of number of deliveries and total breast-feeding time on bone mineral density in premenopausal and young postmenopausal women. Maturitas 2014;77(3):249–54.
[34] Grisso J, Kelsey J, Gammon M, O'Brien L. Parity, lactation and hip fracture. Osteoporos Int 1993;3:171–6.
[35] Alderman BW, WEISS NS, Daling JR, Ure C, Ballard JH. Reproductive history and postmenopausal risk of hip and forearm fracture. Am J Epidemiol 1986;124: 262–7.
[36] O'Neill TW, Silman AJ, Diaz MN, Cooper C, Kanis J, Felsenberg D. Influence of hormonal and reproductive factors on the risk of vertebral deformity in European women. Osteoporos Int 1997;7:72–8.
[37] Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, et al. Risk factors for hip fracture in European women: the MEDOS study. J Bone Miner Res 1995;10: 1802–15.
[38] Bjørnerem Å, Ahmed LA, Jørgensen L, Størmer J, Joakimsen RM. Breastfeeding protects against hip fracture in postmenopausal women: the Tromsø study. J Bone Miner Res 2011;26:2843–50.
[39] Kent GN, Price RI, Gutteridge DH, Allen JR, Barnes MP, Hickling CJ, et al. Human lactation: forearm trabecular bone loss, increased bone turnover, and renal conservation of calcium and inorganic phosphate with recovery of bone mass following weaning. J Bone Miner Res 1990;5:361–9.
[40] Greendale GA, Sowers M, Han W, Huang MH, Finkelstein JS, Crandall CJ, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res 2012;27:111–8.
[41] Mackey DC, Lui L-Y, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, et al. High-trauma fractures and low bone mineral density in older women and men. JAMA: J Am Medi Assoc 2007;298:2381–8.
[42] Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal recall of breastfeeding practice. Nutr Rev 2005;63:103–10.
[43] Tomeo CA, Rich-Edwards JW, Michels KB, Berkey CS, Hunter DJ, Frazier AL, et al. Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology 1999;10:774–6.
[44] Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ (Clin res ed) 1996;312: 1254–9.
[45] Faulkner KG, Wacker W, Barden H, Simonelli C, Burke P, Ragi S, et al. Femur strength index predicts hip fracture independent of bone density and hip axis length. Osteoporos Int 2006;17:593–9.
[46] Dufour A, Roberts B, Broe K, Kiel D, Bouxsein M, Hannan M. The factor-of-risk biomechanical approach predicts hip fracture in men and women: the Framingham Study. Osteoporos Int 2012;23:513–20.
[47] Leslie W, Pahlavan P, Tsang J, Lix L. Prediction of hip and other osteoporotic fractures from hip geometry in a large clinical cohort. Osteoporos Int 2009;20:1767–74.