

**Table 4**  
Association Between Mild and Severe Depression and Their Risk Factors by Multinomial Multiple Logistic Regression (n = 1856)

Variables	Mild Depression (n = 193)		Severe Depression (n = 79)	
	OR 95%CI	P Value	OR 95%CI	P Value
Social engagement				
Living alone	0.374 (0.19–0.74)	.005	0.777 (0.33–1.8)	.566
Eating alone	2.96 (1.8–5.0)	<.001	3.33 (1.6–6.8)	.001
Low reciprocal social support	1.73 (1.0–2.9)	.045	1.66 (0.80–3.4)	.172
Fewer frequency of going out	2.21 (1.5–3.2)	<.001	2.79 (1.6–4.8)	<.001
Major change in life	1.78 (1.2–2.6)	.002	1.63 (0.93–2.9)	.091
Social ties with family	0.940 (0.88–1.0)	.046	0.935 (0.85–1.0)	.162
Social ties with friends	0.929 (0.88–0.98)	.007	0.895 (0.82–0.97)	.009
Sociodemographic variables				
Sex (male)	1.27 (0.78–2.1)	.335	2.46 (1.2–5.0)	.013
Age	0.950 (0.92–0.98)	.005	0.998 (0.95–1.0)	.943
Education (years)	1.05 (0.98–1.1)	.190	1.03 (0.93–1.1)	.582
Health literacy	0.670 (0.52–0.87)	.003	0.440 (0.31–0.63)	<.001
Low income	1.72 (1.1–2.8)	.024	1.65 (0.84–3.3)	.145
Medical histories				
Hypertension	0.743 (0.51–1.1)	.118	1.14 (0.64–2.0)	.655
Cerebrovascular diseases	1.38 (0.74–2.6)	.312	2.36 (1.1–5.2)	.033
Osteoporosis	0.712 (0.43–1.2)	.184	0.839 (0.39–1.8)	.652
Heart diseases	1.00 (0.65–1.5)	.994	1.28 (0.67–2.5)	.461
Number of medications	1.08 (1.0–1.1)	.017	1.10 (1.0–1.2)	.027
Physical health and functions				
IADL	0.834 (0.63–1.1)	.215	0.862 (0.59–1.3)	.446
Mobility	0.983 (0.97–1.0)	.044	0.988 (0.96–1.0)	.327
Cognitive function: MMSE	0.927 (0.85–1.0)	.103	0.994 (0.87–1.1)	.930
Oral health and functions: GOHAI	0.943 (0.92–0.97)	<.001	0.928 (0.90–0.96)	<.001
Nutritional and dietary status				
Food variety	0.959 (0.88–1.0)	.344	0.960 (0.84–1.1)	.531
MNA-SF	0.936 (0.84–1.0)	.251	0.839 (0.72–0.98)	.029

CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.

living arrangement. “Living with others yet eating alone” was a significant predictor of depression for both age groups, with odds ratio reaching as high as 5 times for the young-old. This suggests that eating alone acts as stronger risk factor than living alone, and that the living arrangement in which older adults eat alone can act as a critical determinant of depressive risks. Meals are an important location of socialization whereby older adults enjoy intimate interactions, and when shared with others, they can provide valuable opportunities for companionship and social support.<sup>18</sup> A lack of communication during meals may result in feelings of loneliness and depressed moods.<sup>19</sup>

Table 5 suggests that those who eat alone despite living with their families tend to be the most socially withdrawn, with least awareness of their health conditions and the poorest physical, oral, and cognitive functions as well as nutritional status. The fact that they do not share a single meal with their families despite living together suggests that they have distant relationships with them. Compared with those who eat with others, a greater proportion of those who eat alone live with their children, children-in-law or grandchildren, and less with their spouse. This suggests that they may be eating alone because they lead different life styles, suffer from emotional distance, concerns that they will add burdens on their families if they eat together, or from uncomfortable relationships with family members such as children-in-law. This is supported by the fact that they have the weakest social ties with family. This may result in lower interest in their health shown by their families, as well as in lower self-interest. The fact that they show the lowest health literacy also supports this hypothesis. They also exhibit the lowest mobility and social ties with friends, suggesting that they are the most socially isolated not only at home but also outside. The fact that their gait speeds and IADL are the lowest imply that their poor physical functions play a role in limiting their social activities. GOHAI scores, number of remaining teeth and occlusal force are lowest in this group, indicating the possibility that they eat alone because they eat too slowly, require different menus, or because they have concerns about their oral appearance. The poor oral functions and nutritional/dietary status (low food variety and

MNA-SF scores) may also be another manifestation of the lack of interest in their health shown by their families as well as by themselves.

In any case, the sentiments or perceptions that lead them to eat alone despite living with their families are likely to be negative in nature and may be internally conceived by the older adults themselves, or externally imposed by families living together or the wider society. The functional decline, which may be a cause as well as a result from eating alone, may also contribute to the depressive outcomes.

Stratification by age groups and multinomial regression analysis by different severities of depression revealed that fewer variables of social engagement were associated with depressive outcomes as the population ages or becomes more mentally frail. This suggests that social engagement is a more powerful predictor of mental health at earlier points along geriatric trajectories, and, thus, that effective social preventive measures require early interventions. Lower down the geriatric trajectories, social factors fall in their relative importance and the role of health and functional factors increase. This is suggested by the fact that the number of medications becomes a significant predictor for old-old, and the history of cerebrovascular diseases and MNA-SF scores become significant for severe depression.

Outside the domain of social engagement, the independent risk factors for depressive symptoms in both age groups included GOHAI and health literacy, supporting the findings of previous studies.<sup>36–38</sup> Uniquely for young-old, mobility, MNA-SF, and income were associated. For old-old only, the number of medications remained a predictor of depressive symptoms.

This study elucidates that reducing the risk of depression requires much more than medical care and that preventive measures need to be introduced early on in the geriatric trajectories, before frailty sets in. The present study shows that social factors such as eating alone pose substantial risk for mental health. Comprehensive assessment that covers a wide range of health-related domains including physical health, oral functions, nutritional, and dietary status as well as social relations will be necessary to identify those at risk effectively.

**Table 5**  
Characteristics by Living and Eating Arrangement (n = 1856)

Variables	Living and Eating Alone (n = 160)	Living Alone Yet Eating With Others (n = 36)	Living with Others Yet Eating Alone (n = 111)	Living and Eating With Others (n = 1549)	P Value*
	Mean ± SD or n (%)				
<b>Social engagement</b>					
Live with spouse	—	—	61 (55.0)	1393 (89.9)	<.001
Live with children	—	—	74 (66.7)	627 (40.5)	<.001
Live with children-in-law	—	—	21 (18.9)	117 (7.6)	<.001
Live with grand-children	—	—	29 (26.1)	171 (11.0)	<.001
Social ties with family	7.24 ± 3.4	8.83 ± 3.5	7.19 ± 3.2	8.19 ± 3.1	<.001*
Social ties with friends	8.08 ± 3.4	8.86 ± 2.9	6.86 ± 4.0	8.19 ± 3.6	.003*
<b>Sociodemographic variables</b>					
Sex (male)	42 (26.3)	11 (30.6)	63 (56.8)	812 (52.4)	<.001
Age	74.6 ± 6.0	75.4 ± 5.2	75.3 ± 5.7	72.5 ± 5.3	<.001*
Education (years)	11.9 ± 2.7	12.0 ± 2.7	11.8 ± 3.2	12.9 ± 2.7	<.001*
Health literacy	3.87 ± 0.71	4.13 ± 0.71	3.86 ± 0.66	4.01 ± 0.62	.015
Number of medications	3.50 ± 3.5	4.17 ± 4.3	3.76 ± 3.7	2.79 ± 2.9	.004
<b>Physical health and functions</b>					
Usual gait speed (m/s)	1.43 ± 0.25	1.44 ± 0.26	1.41 ± 0.27	1.48 ± 0.25	.026
Max gait speed (m/s)	2.05 ± 0.38	2.03 ± 0.46	2.01 ± 0.36	2.17 ± 0.39	<.001*
IADL	4.94 ± 0.30	4.94 ± 0.23	4.69 ± 0.84	4.86 ± 0.46	.007
Mobility	23.9 ± 10	27.3 ± 11	21.0 ± 11	24.9 ± 9.9	<.001*
<b>Mental health</b>					
GDS	3.18 ± 3.4	2.86 ± 3.2	4.83 ± 4.1	2.39 ± 2.7	<.001*
Depressive symptoms: GDS ≥6	31 (19.4)	4 (11.1)	45 (40.5)	192 (12.4)	<.001
Severe depression: GDS ≥10	12 (7.5)	4 (11.1)	17 (15.3)	46 (3.0)	<.001
Cognitive function: MMSE	28.3 ± 1.8	28.0 ± 1.6	27.8 ± 1.9	28.2 ± 1.8	.029
<b>Oral health and functions</b>					
GOHAI	53.8 ± 7.3	53.3 ± 7.8	53.1 ± 6.6	54.9 ± 6.2	<.001*
Number of remaining teeth	20.5 ± 8.0	19.2 ± 8.4	17.8 ± 9.7	21.0 ± 8.3	.003*
Occlusal force (N)	496 ± 333	522 ± 365	478 ± 345	585 ± 361	<.001*
<b>Nutritional and dietary status</b>					
BMI (kg/m <sup>2</sup> )	22.3 ± 3.3	24.3 ± 3.6	22.8 ± 3.3	22.9 ± 2.9	.002
Food variety	3.74 ± 2.0	3.89 ± 2.0	3.26 ± 2.1	3.79 ± 2.0	.037
MNA-SF	12.2 ± 1.6	12.4 ± 1.6	12.1 ± 1.7	12.5 ± 1.4	.007

Those continuous variables that showed significant difference between “living with others yet eating alone” and “living and eating with others” in the multiple comparison test (Dunnnett T3) are highlighted with “\*\*\*”.

\*Kruskal-Wallis test for continuous variables and  $\chi^2$  test for categorical variables.

The limitations of our study are mainly 4-fold. First, the cross-sectional nature of the study prevents it from making any conclusive comments about the causality between independent variables and the outcome. Second, data on household income were not available, and instead, individual income was used. Given that the older adults in the present study grew up in a period when it was rare for women to work after marriage, household income would have been a better indicator of the economic environment for women. Third, depressive symptoms were measured using self-administered GDS questionnaire rather than diagnosis by physicians. Fourth, the participants inevitably comprised those who had greater degrees of interest in health and lower barriers to participation in the study. This may have skewed the nature of participants, to those who were more socially active and interested in health, missing out those who were most socially disengaged.

## Conclusions

For community-dwelling Japanese older adults, depressive symptoms were significantly associated with social engagement, with greater associations in younger and less mentally frail populations. Eating alone was identified as a key risk factor for depressive symptoms, and those who live with their families yet eat their meals alone were at highest risk. Mental health management for older adults, therefore, requires comprehensive assessment of their social relations, taking into account their companionship during mealtimes. Social preventive measures need to involve early interventions in order to augment their effectiveness against mental frailty.

Given that depression can lay the ground for further frailty and

various detrimental health outcomes, further study with a longitudinal design, with more detailed data collection on social predictors of depression, may play a pivotal role in identifying possible intervention opportunities to prevent not only mental but also physical frailties.

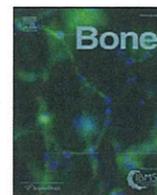
## Acknowledgments

The authors thank the staff members and participants of the Kashiwa study and the following individuals for helping with the acquisition of data: Dr Takashi Higashiguchi, Fujita Health University School of Medicine; Dr Kazuko Ishikawa-Takata RD, National Institute of Health and Nutrition; Dr Yoshiya Oishi PhD DDS, Oishi Dental Clinic; Dr Noriaki Takahashi, The Nippon Dental University; Seigo Mitsutake, Tokyo Metropolitan Institute of Gerontology; and staff members of The Institute of Healthcare Innovation Project, The University of Tokyo.

## References

- Djernes JK. Prevalence and predictors of depression in populations of elderly: A review. *Acta Psychiatr Scand* 2006;113:372–387.
- Schwarzbach M, Luppia M, Forstmeier S, et al. Social relations and depression in late life—A systematic review. *Int J Geriatr Psychiatry* 2014;29:1–21.
- Muramatsu N, Akiyama H. Japan: Super-aging society preparing for the future. *Gerontologist* 2011;51:425–432.
- Wada T, Ishine M, Sakagami T, et al. Depression in Japanese community-dwelling elderly—Prevalence and association with ADL and QOL. *Arch Gerontol Geriatr* 2004;39:15–23.
- Blazer DG, Hybels CF. Origins of depression in later life. *Psychol Med* 2005;35:1241–1252.

6. Park NS, Jang Y, Lee BS, et al. The mediating role of loneliness in the relation between social engagement and depressive symptoms among older Korean Americans: Do men and women differ? *J Gerontol B Psychol Sci Soc Sci* 2013; 68:193–201.
7. Beekman ATF, Deeg DJH, vanTilburg T, et al. Major and minor depression in later life: A study of prevalence and risk factors. *J Affect Disord* 1995;36: 65–75.
8. Fukunaga R, Abe Y, Nakagawa Y, et al. Living alone is associated with depression among the elderly in a rural community in Japan. *Psychogeriatrics* 2012; 12:179–185.
9. Kawachi I, Berkman LF. Social ties and mental health. *J Urban Health* 2001;78: 458–467.
10. Heun R, Hein S. Risk factors of major depression in the elderly. *Eur Psychiatry* 2005;20:199–204.
11. Mendes de Leon CF. Social engagement and successful aging. *Eur J Ageing* 2005;2:64–66.
12. Park NS. The relationship of social engagement to psychological well-being of older adults in assisted living facilities. *J Appl Gerontol* 2009;28:461–481.
13. Tilvis RS, Routasalo P, Karppinen H, et al. Social isolation, social activity and loneliness as survival indicators in old age; A nationwide survey with a 7-year follow-up. *Eur Geriatr Med* 2012;3:18–22.
14. Tomaka J, Thompson S, Palacios R. The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. *J Aging Health* 2006;18:359–384.
15. Avlund K, Lund R, Holstein BE, Due P. Social relations as determinant of onset of disability in aging. *Arch Gerontol Geriatr* 2004;38:85–99.
16. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med* 1999;131:165–173.
17. Bath PA, Deeg D. Social engagement and health outcomes among older people: Introduction to a special section. *Eur J Ageing* 2005;2:24–30.
18. Vesnaver E, Keller HH. Social influences and eating behavior in later life: A review. *J Nutr Gerontol Geriatr* 2011;30:2–23.
19. Kimura Y, Wada T, Okumiya K, et al. Eating alone among community-dwelling Japanese elderly: Association with depression and food diversity. *J Nutr Health Aging* 2012;16:728–731.
20. Markle-Reid M, Browne G. Conceptualizations of frailty in relation to older adults. *J Adv Nurs* 2003;44:58–68.
21. Schreiner AS, Hayakawa H, Morimoto T, Kakuma T. Screening for late life depression: Cut-off scores for the Geriatric Depression Scale and the Cornell Scale for Depression in Dementia among Japanese subjects. *Int J Geriatr Psychiatry* 2003;18:498–505.
22. Crooks VC, Lubben J, Petitti DB, et al. Social network, cognitive function, and dementia incidence among elderly women. *Am J Public Health* 2008;98: 1221–1227.
23. Lubben J, Blozik E, Gillmann G, et al. Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *Gerontologist* 2006;46:503–513.
24. Ishikawa H, Nomura K, Sato M, Yano E. Developing a measure of communicative and critical health literacy: A pilot study of Japanese office workers. *Health Promot Int* 2008;23:269–274.
25. Liu CP, Leung DS, Chi I. Social functioning, polypharmacy and depression in older Chinese primary care patients. *Aging Ment Health* 2011;15: 732–741.
26. Koyano W, Shibata H, Nakazato K, et al. Measurement of competence—Reliability and validity of the TMIG index of competence. *Arch Gerontol Geriatr* 1991;13:103–116.
27. Baker PS, Bodner EV, Allman RM. Measuring life-space mobility in community-dwelling older adults. *J Am Geriatr Soc* 2003;51:1610–1614.
28. Peel C, Baker PS, Roth DL, et al. Assessing mobility in older adults: The UAB Study of Aging Life-Space Assessment. *Phys Ther* 2005;85:1008–1019.
29. Shimada H, Sawyer P, Harada K, et al. Predictive validity of the classification schema for functional mobility tests in instrumental activities of daily living decline among older adults. *Arch Phys Med Rehabil* 2010;91:241–246.
30. Shimada H, Ishizaki T, Kato M, et al. How often and how far do frail elderly people need to go outdoors to maintain functional capacity? *Arch Gerontol Geriatr* 2010;50:140–146.
31. Ishii S, Tanaka T, Shibasaki K, et al. Development of a simple screening test for sarcopenia in older adults. *Geriatr Gerontol Int* 2014;14:93–101.
32. Atchison KA, Dolan TA. Development of the geriatric oral health assessment index. *J Dent Educ* 1990;54:680–687.
33. Naito M, Suzukamo Y, Nakayama T, et al. Linguistic adaptation and validation of the General Oral Health Assessment Index (GOHAI) in an elderly Japanese population. *J Public Health Dent* 2006;66:273–275.
34. Kumagai S, Watanabe S, Shibata H, et al. Effects of dietary variety on declines in high-level functional capacity in elderly people living in a community. *Nihon Kosho Eisei Zasshi* 2003;50:1117–1124.
35. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56:M366–M372.
36. Hassel AJ, Danner D, Schmitt M, et al. Oral health-related quality of life is linked with subjective well-being and depression in early old age. *Clin Oral Investig* 2011;15:691–697.
37. de Andrade FB, Lebrao ML, Santos JLF, et al. Relationship between oral health-related quality of life, oral health, socioeconomic, and general health factors in elderly Brazilians. *J Am Geriatr Soc* 2012;60:1755–1760.
38. Gazmararian J, Baker D, Parker R, Blazer DG. A multivariate analysis of factors associated with depression: Evaluating the role of health literacy as a potential contributor. *Arch Intern Med* 2000;160:3307–3314.



## 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 <sup>a,\*</sup>, Shinya Ishii <sup>b</sup>, Gail A. Greendale <sup>c</sup>, Jane A. Cauley <sup>d</sup>, Kristine Ruppert <sup>d</sup>, Carolyn J. Crandall <sup>e</sup>, Arun S. Karlamangla <sup>c</sup>

<sup>a</sup> Department of Medicine/Division of General Internal Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba 296-8602, Japan

<sup>b</sup> Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

<sup>c</sup> Department of Medicine/Division of Geriatrics, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, Ste. 2339, Los Angeles CA 90095, USA

<sup>d</sup> Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A510 Crabtree Hall, Pittsburgh, PA 15260, USA

<sup>e</sup> 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.

© 2015 Elsevier Inc. All rights reserved.

## 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 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: [takahirokori@outlook.com](mailto:takahirokori@outlook.com) (T. Mori).

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

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

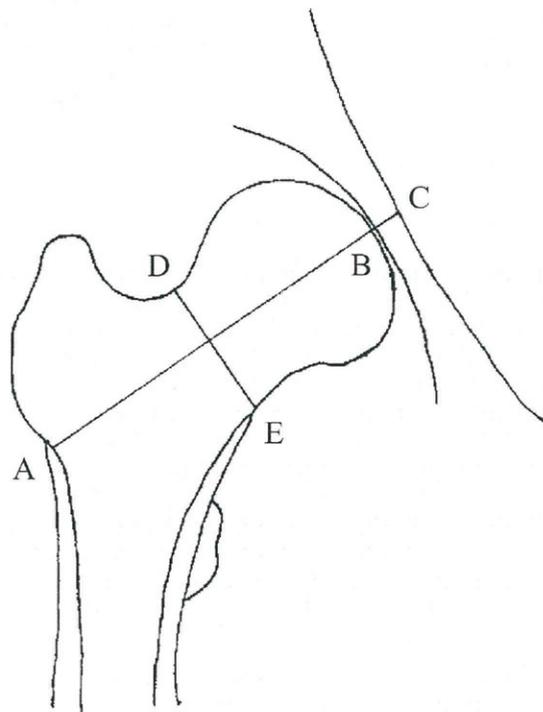
$$\text{Bending strength index (BSI)} = \text{BMD} * (\text{FNW})^2/(\text{FNAL} * \text{weight})$$

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

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 pump 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 kilograms 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 pump 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 fractures 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 pump 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<sup>a</sup> of the study participants at baseline.<sup>b</sup>

Characteristics	Study sample with composite indices of femoral neck strength data (n = 1881 <sup>c</sup> )	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 <sup>2</sup> )	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 <sup>d</sup>	50 (2.7%)	57 (2.5%)
Medication use ever (till 12th follow-up) <sup>e</sup>		
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 <sup>d</sup>	312 (16.6%)	350 (15.6%)
Physical activity score (ranging from 4 to 20) <sup>f</sup>	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 <sup>2</sup> )	0.83 [0.74, 0.92]	0.84 [0.75, 0.93]
Lumbar spine bone mineral density (g/cm <sup>2</sup> )	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]	-

<sup>a</sup> Median and interquartile range for continuous variables and number of participants and percentage for categorical variables.

<sup>b</sup> All characteristics reported were measured at baseline except the 'medication use ever' variables, which were used in the fracture analysis.

<sup>c</sup> 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).

<sup>d</sup> Included antiepileptic medications, chemotherapy, gonadotropin-releasing hormone agonist, aromatase inhibitors, or thiazolidinediones.

<sup>e</sup> Any use including either prior or at baseline, or during the follow-up till visit 12.

<sup>f</sup> 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: 0.06, 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<sup>2</sup> (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:  $-0.017$ SD, 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<sup>a</sup> associations<sup>b</sup> (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.

<sup>a</sup> 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.

<sup>b</sup> 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

- Specker BL. Bone mineral changes during pregnancy and lactation. *Endocrine* 2002; 17:49–53.
- Karlsson MK, Ahlborg HG, Karlsson C. Female reproductive history and the skeleton – a review. *BJOG: Int J Obstet Gynaecol* 2005;112:851–6.
- Møller U, við Streym S, Mosekilde L, Rejnmark L. Changes in bone mineral density and body composition during pregnancy and postpartum. A controlled cohort study. *Osteoporos Int* 2012;23:1213–23.
- 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.
- 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.
- 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.
- Specker B, Binkley T. High parity is associated with increased bone size and strength. *Osteoporos Int* 2005;16:1969–74.
- Wiklund P, Xu L, Wang Q, Mikkola T, Lyytikäinen A, Völggi E, et al. Lactation is associated with greater maternal bone size and bone strength later in life. *Osteoporos Int* 2012;23:1939–45.
- Laskey M, Price R, Khoo B, Prentice A. Proximal femur structural geometry changes during and following lactation. *Bone* 2011;48:755–9.
- Gunderson EP. Childbearing and obesity in women: weight before, during, and after pregnancy. *Obstet Gynecol Clin North Am* 2009;36:317–32.
- 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.
- 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.
- 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.
- 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.
- Karlmanla 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.
- Ishii S, Greendale 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.
- 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.
- Ishii S, Cauley J, Greendale G, Danielson M, Nili NS, Karlmanla A. Ethnic differences in composite indices of femoral neck strength. *Osteoporos Int* 2012;23:1381–90.
- Heaney R, Abrams S, Dawson-Hughes B, Looker A, Looker A, Marcus R, et al. Peak bone mass. *Osteoporos Int* 2000;11:985–1009.
- 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.
- 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.
- 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].
- 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.
- 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.
- 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.
- Horton NJ, Lipsitz SR. Multiple imputation in practice: comparison of software packages for regression models with missing variables. *Am Stat* 2001;55:244–54.
- Heitjan DF, Little RJ. Multiple imputation for the fatal accident reporting system. *Appl Stat* 1991;13–29.
- 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.
- 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.
- 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.
- 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.
- Dursun N, Akin S, Dursun E, Sade I, Korkusuz F. Influence of duration of total breast-feeding 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.
- 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.
- Grisso J, Kelsey J, Gammon M, O'Brien L. Parity, lactation and hip fracture. *Osteoporos Int* 1993;3:171–6.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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 Med Assoc* 2007;298:2381–8.
- Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal recall of breastfeeding practice. *Nutr Rev* 2005;63:103–10.
- 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.
- 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.
- 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.
- 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.
- 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.