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ORIGINAL ARTICLE

Parity and lactation are not associated with incident fragility fractures or radiographic vertebral fractures over 16 years of follow-up: Canadian Multicentre Osteoporosis Study (CaM*os*)

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Abstract

Summary Parity and lactation showed no associations with incident clinical fragility fractures or radiographic vertebral compression fractures in the 16-year CaM*os* prospective study. Parity was associated with slightly greater decline in femoral neck but not hip or spine areal bone mineral density (aBMD), while lactation showed no associations with aBMD change.

Purpose Pregnancy and especially lactation cause loss of bone mass and microarchitectural changes, which temporarily increase fracture risk. After weaning, aBMD increases but skeletal microarchitecture may be incompletely restored. Most retrospective clinical studies found neutral or even protective associations of parity and lactation with fragility fractures, but prospective data are sparse. CaM*os* is a randomly selected observational cohort that includes ~6500 women followed prospectively for over 16 years.

Methods We determined whether parity or lactation were related to incident clinical fragility fractures over 16 years, radiographic (morphometric and morphologic) vertebral fractures over 10 years, and aBMD change (spine, total hip, and femoral neck) over 10 years. Parity and lactation duration were analyzed as continuous variables in predicting these outcomes using univariate and multivariate regression analyses.

Results Three thousand four hundred thirty-seven women completed 16 years of follow-up for incident clinical fractures, 3839 completed 10 years of morphometric vertebral fracture assessment, 3788 completed 10 years of morphologic vertebral fracture assessment, and 4464 completed 10 years of follow-up for change in aBMD. In the multivariate analyses, parity and lactation duration showed no associations with clinical fragility fractures, radiographic vertebral fractures, or change in aBMD, except that parity associated with a probable chance finding of a slightly greater decline in femoral neck aBMD.

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Conclusions Parity and lactation have no adverse associations with clinical fragility or radiographic vertebral fractures, or the rate of BMD decline over 10 years, in this prospective, multicenter study of a randomly selected, population-based cohort of women.

Keywords Pregnancy · Lactation · Postmenopause · Fractures · Nutrition · Osteoporosis

Introduction

The skeleton is a storehouse of minerals. Physiological demand for calcium can induce substantial bone resorption, which in turn reduces skeletal strength and may precipitate fractures. Pregnancy, lactation, egg laying, and antler formation invoke such physiological resorption to provide minerals respectively to the fetus, neonate, egg shell, and antlers [1].

Human physiology adapts during pregnancy to provide about 30 g of calcium, 20 g of phosphorus, and 0.8 g of magnesium to a full-term singleton [1]. Although most of that mineral is obtained by upregulation of the mother's intestinal absorption of calcium and phosphate, some resorption of the maternal skeleton also occurs, especially in women with low calcium intakes [1]. More marked resorption occurs during lactation, with trabecular bone preferentially resorbed during the first 6 months of lactation to provide about 200 mg of calcium daily for breast milk [2]. This leads to 5–10% decreases in areal bone mineral density (aBMD) of the lumbar spine, and smaller losses at more cortical sites (hip, forearm, total hip, whole body) [1]. High-resolution peripheral computed tomography (HR-pQCT) studies in women [3, 4], and histomorphometric studies in animals [1, 5, 6], have demonstrated lactational resorption of trabecular and cortical bone, substantially increased osteoclast numbers, and osteocytic osteolysis. These lactational changes increase the risk of vertebral compression fractures occurring during the postpartum period, although such fractures are rare [7].

After lactation ceases (weaning), aBMD of the lumbar spine and hip spontaneously recover after 6 to 12 months to prepregnancy values or higher [1], whereas limited HR-pQCT studies of the tibial shaft or distal radius have found that the skeletal microarchitecture may remain incompletely recovered at those sites [3, 4]. High-resolution imaging and histomorphometric studies in animals have confirmed that the magnitude of recovery varies by skeletal site, with complete recovery at the vertebrae but residual deficits (largely reduced trabecular number) at appendicular sites [1, 8–11]. This recovery proceeds through an upregulation in osteoblast number and function, while osteocytes restore mineral content to their lacunae [1].

What are the long-term consequences of these reproductive changes in skeletal mineralization and architecture? In rodents, the breaking strength of vertebrae and appendicular bone return to prepregnancy values within 2 to 4 weeks [1, 10–12]. In women, more than six dozen cross-sectional and retrospective epidemiological studies have found that parity and lactation have neutral or even protective associations with low aBMD, osteoporosis diagnosis, or fractures [1, 13, 14]. However, these studies were largely retrospective and small. The Women's Health Initiative observational cohort reported prospective data from 92,980 evaluable postmenopausal women over a mean of 7.9 years and found that parity and lactation were not associated with self-reported hip or other clinical fractures, nor (in a subset of women) with change in aBMD [15]. However, when analyzed categorically against women who had never breastfed, lactation for at least 1 month was associated with a 15% lower risk of hip fractures [15]. Only 5919 subjects (6.3% of the cohort) had aBMD measurements, but no radiographic data to document vertebral morphometric deformities or morphological fractures were obtained. Since the trabecular-rich spine loses aBMD most rapidly during lactation, and 75–80% of vertebral compression fractures are silent, an analysis limited to clinical fractures overlooks part of the potential fracture burden.

The purpose of this study was to determine whether parity or lactation were associated with incident clinical fragility fractures, incident radiographic (morphometric and morphologic) spine fractures, or rate of change in aBMD in a randomly selected cohort of women who participated in the prospective Canadian Multicentre Osteoporosis Study (CaM*os*). This report analyzed 16 years of prospective incident clinical fracture data, 10 years of radiographic vertebral fracture data, and 10 years of change in aBMD.

Materials and methods

Subjects and setting

This is an analysis of data from CaM*os*, which began in 1995 as a randomly selected, prospective, population-based observational cohort study. Community-dwelling women and men living within 50 km of nine urban centers in Canada were recruited randomly from residential telephone lists. Recruitment was age stratified with increasing numbers at older ages so the mean age at baseline was ~ 63 years (range 25 to 103). The sites included St John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver. Of those randomly selected individuals, 42% gave informed consent to full participation, including clinical

assessments. The study design, population sampling method, and detailed questionnaires have been previously published [16]. CaM*os* was approved by the Ethics Committee of McGill University and each participating center.

Data collection

Participants completed a standardized interviewer-administered questionnaire (CaM*os* questionnaire ©1995) at baseline, which assessed demographics, general health, nutrition, medical history, lifestyle factors (smoking, alcohol, exercise), reproductive and lactation history, and medication use. The questionnaire targeted risk factors for fractures. Additional assessments included anthropometric measurements, aBMD by dual X-ray absorptiometry, and (in participants age 50 and older) lateral spine radiographs.

Follow-up annual postal questionnaires were self-administered yearly, except during years when follow-up interviewer-administered questionnaires and aBMD measures were completed: years 3 (for those ages 40–60 at baseline), 5, and 10. Follow-up spine radiographs were obtained at years 5 and 10 for all participants aged 50 and older; annual fracture questionnaires and validation continued for all remaining cohort participants through year 16. Deaths were confirmed by contact with the next of kin or proxy, or by review of obituaries.

Reproductive variables included number of pregnancies, parity (number of live births), total months of recalled lactation, age of menopause (date of last menstrual flow), prior use of hormonal contraceptives, ovarian hormone therapy, and then a specification as to whether it involved estrogen, progestin, or both. Women who answered "yes" to ever breastfeeding were instructed to indicate the total number of months they had breastfed all children combined. In that questionnaire, recalled breastfeeding of 1 month or longer qualified as any lactation, while lactation for less than 1 month was considered no lactation.

The CaMos questionnaire assessed other lifestyle variables including physical activity, nutrition (calcium and vitamin D intakes from diet and supplements), smoking, alcohol, and other medical conditions. A subset of subjects had measurements of 25-hydroxyvitamin D [17].

All women in the CaM*os* cohort were eligible for inclusion in this analysis.

aBMD measurement

Lumbar spine (L1–L4), femoral neck, and total hip aBMD were measured by DXA using Hologic QDR (Marlborough, MA, USA) or Lunar DPX (Piscataway, NJ, USA) densitometers. Seven of the nine centers used Hologic machines. Details of methodology, quality assurance, and conversion of Lunar into equivalent Hologic units have been previously published [18]. All densitometers were calibrated at the start of the study and once each year thereafter using the Bona Fide Spine Phantom (BFP, Bio-Imaging Technologies, Newtown, PA, USA) to ensure site-to-site comparability.

Fracture assessment

Prevalent clinical fractures were self-reported by degree of trauma and site at baseline, while incident clinical fractures were reported on yearly follow-up postal and interviewer-administered surveys. When clinical fractures were identified by interviewer-administered questionnaire or annual postal survey, a structured interview (in person or by telephone, respectively) was carried out to determine and confirm the date, site, circumstances, degree of trauma, and management of the fracture. Whenever fracture questionnaires were not completed (including in those who died), secondary contact information was used to complete the fracture questionnaire by proxy. Independent medical records were obtained with consent and medically confirmed 78% of all incident fractures (e.g., hip vs. non-hip leg) [18]; those remaining unconfirmed were due to inability to obtain the records. To avoid underestimating the numbers of fractures, we included all self-reported fractures that were disclosed in the structured telephone interviews.

Fragility fractures were defined as those involving a force less than or equal to a fall from a standing height. In this osteoporosis-specific definition, we included clinical osteoporotic fractures of the hip, spine, forearm, humerus, ribs, and pelvis. We excluded incident fractures of the skull, face, hands, ankles, and feet.

Spine radiographs (from T4 to L4) at years 5 and 10 were used to identify incident vertebral compression fractures or deformities as compared to baseline radiographs at year 0; the detailed methodology has previously been published [19]. In brief, the morphometric or Genant semiquantitative (GSQ) method was used to identify > 20% vertebral height reduction, classified as 20 to 25% (grade 1, GSQ1), 26 to 40% (grade 2, GSQ2), and > 40% (grade 3, GSQ3) in the anterior, midpoint, and posterior heights of the vertebral body [20]. The second, morphologic approach used a modification of the algorithm-based qualitative (ABQ) tool, in which endplate fracture is used as the primary qualitative indicator of a vertebral compression fracture [21]. The modified ABQ (mABQ) method included endplate depression with anterior cortical fractures or buckling, and graded the degree of vertebral height reduction according to the GSQ method, in order to make the results semiquantitative [19]. We compared both methods because the morphometric GSQ method has been most widely used in the literature, whereas fractures detected by the newer, morphologic mABQ algorithm correlate more closely with known risk factors for fragility fractures, including low aBMD [19].

Statistical analysis

The primary outcome was any clinical fragility fractures over 16 years, collectively and then separately, at six skeletal sites (forearm, ribs, spine, hip, shoulder, pelvis). The secondary outcomes were radiographic (morphometric and morphologic) vertebral compression fractures over 10 years, and change in aBMD over 10 years at the lumbar spine, total hip, and femoral neck.

Parity and lactation duration were analyzed as continuous variables in predicting total incident clinical fragility fractures over 16 years, radiographic vertebral fractures over 10 years, and change in aBMD at the lumbar spine, total hip, and femoral neck over 10 years. Continuous was defined as the spectrum from nulliparity to grand multiparity, and from zero to the maximum number of months of recalled breastfeeding.

Descriptive statistics were provided for all variables, mean/standard deviation, and count/frequency for continuous and categorical variables, respectively. Univariate and multivariate Cox regression were conducted to identify significant risk factors associated with clinical fragility fractures over 16 years (all fractures collectively, and then separately for each of the six fracture sites). The significant risk factors associated with radiographic GSQ and mABQ vertebral fractures were identified using logistic regression in univariate and multivariate analysis. Multiple linear regression was used to identify significant risk factors associated with change in aBMD over 10 years at the lumbar spine, total hip, and femoral neck. Only clinically important factors and those variables with a p value of < 0.20 in the univariate analyses were included in the multivariate regression model. Stepwise regression was used to build our final model.

SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

Results

Of the 9423 participants recruited in CaM*os*, 6539 were women. Of these, 3437 were included in the 16-year analysis of clinical fragility fractures, 3839 were included in the 10-year GSQ analysis, 3788 were included in the 10-year mABQ analysis, and 4464 were included in the 10-year analysis of change in aBMD. The flow diagram in Fig. 1 indicates reasons for exclusion from each of these cohorts, with loss to follow-up (including death) accounting for the majority. We also excluded clinical fractures at baseline, and women who had given birth within 12 months of the time of the baseline or a subsequent aBMD measurement, since pregnancy and especially lactation cause transient effects on aBMD [1].

Baseline characteristics of participants in each of the four analyses are shown in Table 1. At study entry, the mean age was 58 with approximately 20% being premenopausal, but in cohorts 2 and 3, the mean age was 65 with only 5.9% being premenopausal. This is due to the radiographs being obtained only in women age 50 or older. About 55–58% of women reported at least 1 month of breastfeeding, with a mean duration of 12 months, and range from 1 to 140 months.

Over 16 years of follow-up of 3437 women, 633 (18.4%) experienced one or more clinical fragility fractures. These

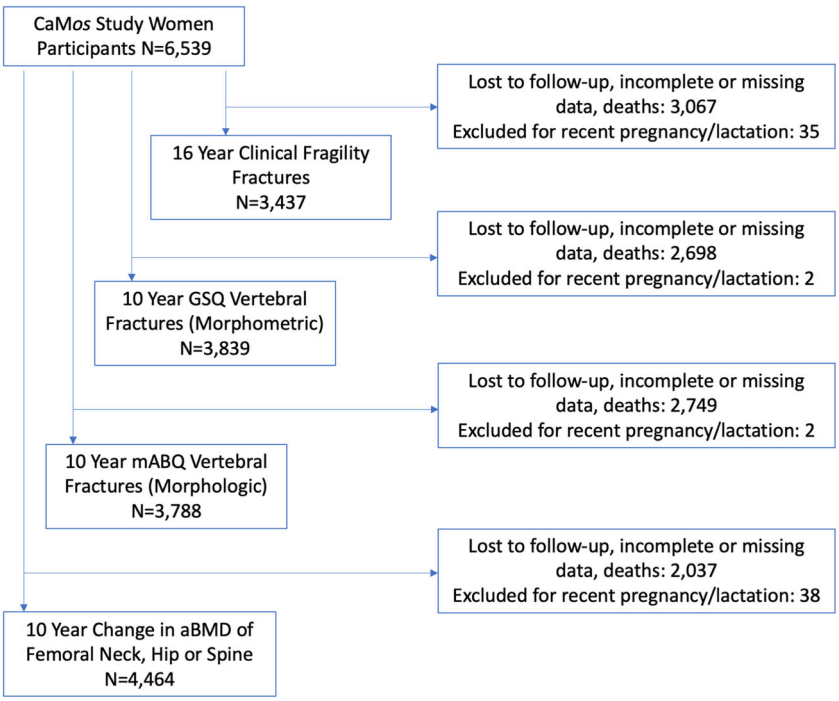

Fig. 1 Flowchart showing disposition of women for each of the analyses

Table 1 Baseline characteristics of the cohorts

Variable	16-year all clinical fractures Mean (SD) or *N* (%)	10-year GSQ vertebral fractures (morphometric) Mean (SD) or *N* (%)	10-year mABQ vertebral fracture (morphologic) Mean (SD) or *N* (%)	10-year change in aBMD of femoral neck, total hip, or spine Mean (SD) or *N* (%)
N	3437	3839	3788	4464
Age	58.4 (11.0)	65.5 (8.8)	65.4 (8.7)	60.6 (11.8)
BMI (kg/m^2)	27 (5.0)	27 (5.0)	27 (5.0)	27 (5.1)
Race/ethnicity				
White	3295 (96.9)	3687 (96.0)	3637 (96.0)	4296 (96.2)
Chinese	69 (2.0)	76 (2.0)	76 (2.0)	80 (1.8)
Black	15 (0.5)	19 (0.5)	19 (0.5)	21 (0.5)
Other	57 (1.7)	57 (1.5)	56 (1.5)	67 (1.5)
Education				
High school or less	1630 (47.4)	2141 (55.8)	2103 (55.5)	2267 (50.1)
Trades or university	1807 (52.6)	1698 (44.2)	1685 (44.5)	2197 (49.9)
Reproductive history				
Age at menarche	13 (1.6)	13. (1.6)	13 (1.6)	13 (1.6)
Age at menopause	47 (6.8)	47 (6.6)	47 (6.6)	47 (6.8)
Not menopausal	781 (22.7)	227 (5.9)	225 (5.9)	883 (19.6)
Menopausal	1653 (48.1)	2276 (59.2)	2247 (59.3)	2248 (49.9)
Oophorectomy	1002 (29.2)	1336 (34.8)	1318 (34.8)	1370 (30.4)
Hormonal contraceptive ever used	2044 (559.5)	2194 (47.2)	2157 (47.0)	2425 (53.9)
No hormonal contraceptive use	1393 (40.5)	1645 (42.8)	1631 (43.0)	2077 (46.1)
Age at first parturition	25 (4.6)	25 (4.5)	25 (4.5)	25 (4.6)
Parity	3 (1.6)	3 (1.8)	3 (1.7)	3 (1.7)
Never breasted	1211 (41.5)	1475 (44.4)	1458 (44.5)	1593 (42.1)
Breastfed	1710 (58.5)	1844 (55.6)	1816 (56.5)	2195 (57.9)
Breastfeeding duration (months)	11.8 (12.2)	12 (12.7)	12 (12.6)	11.7 (12.2)
Breastfed never or ≤ 1 month	1370 (45.0)	1654 (50.0)	1633 (49.9)	1810 (47.8)
Breastfed 2–6 months	596 (20.4)	628 (18.9)	621 (19.0)	758 (20.0)
Breastfed > 6 months	950 (32.6)	1033 (31.2)	1016 (31.1)	1216 (32.1)
Nutrition and habits				
Calcium intake (mg)	1067 (615)	1087 (637)	1087 (637)	1072 (626)
Vitamin D intake (mcg)	7.7 (26.5)	7.9 (16.7)	7.8 (15.5)	7.8 (27.4)
Alcohol (drinks per week)	2.2 (3.8)	2.0 (3.9)	2.0 (4.0)	2.2 (3.9)
Current smoker	929 (14.3)	515 (13.4)	512 (13.5)	584 (13.0)
Past smoker	2127 (32.7)	1322 (34.4)	1303 (34.4)	1492 (33.1)
Never smoked	3441 (53.0)	2002 (52.2)	1973 (52.1)	2426 (53.9)
Exercise				
Exercise (kcal/week)	4676 (3336)	4351 (3141)	4365 (3140)	4546 (3290)
Sedentary hours per day	13.8 (3.0)	13.6 (2.9)	13.6 (2.9)	13.8 (3.0)

Table 1 (continued)

Variable	16-year all clinical fractures Mean (SD) or *N* (%)	10-year GSQ vertebral fractures (morphometric) Mean (SD) or *N* (%)	10-year mABQ vertebral fracture (morphologic) Mean (SD) or *N* (%)	10-year change in aBMD of femoral neck, total hip, or spine Mean (SD) or *N* (%)
Osteoporosis history				
Prevalent fracture	1307 (38)	1666 (57)	1639 (43)	1789 (40)
No prior fractures	2130 (62)	2173 (43)	2151 (57)	2675 (60)
Anti-resorptive current use	993 (28.9)	1138 (29.6)	1124 (29.7)	1240 (27.8)
Anti-resorptive never used	2444 (71.1)	2701 (70.4)	2664 (70.3)	3224 (72.2)
Estrogen-current use	981 (28.5)	1093 (28.5)	1081 (28.5)	1199 (26.9)
Estrogen-past use	514 (15.0)	785 (20.4)	776 (20.4)	738 (16.5)
Estrogen-never used	1942 (56.5)	1961 (51.0)	1931 (51.1)	2527 (56.6)
Progesterone-current use	379 (11.0)	393 (10.2)	388 (10.2)	449 (10.1)
Progesterone-past use	274 (7.9)	276 (7.2)	274 (7.2)	326 (7.3)
Progesterone-never used	2784 (81.0)	3170 (82.6)	31,266 (82.5)	3689 (82.6)

included 188 forearm, 114 rib, 79 clinical spine, 84 hip, 77 shoulder, and 33 pelvic fractures. Over 10 years of follow-up, 3839 women had a full set of evaluable radiographs for the GSQ method, of whom 98 (2.6%) experienced one or more incident deformities or fractures. With the mABQ method, 3788 women had a full set of evaluable radiographs and 83 (2.2%) experienced incident deformities or fractures.

The results of the multivariate analyses for clinical fragility and radiographic spine fractures are shown in Table 2. There were no associations with clinical fragility fractures over 16 years, nor with radiographic mABQ or GSQ vertebral fractures over 10 years. Examination of the six sites of clinical fractures also revealed no associations with parity or lactation (Supplementary Table 1).

Finally, change in aBMD at three skeletal sites over 10 years showed no significant associations with lactation (Table 3). There was a small adverse association of parity with an increased rate of decline in aBMD of the femoral neck (0.0176 g/cm^2 per live birth over 10 years, $p < 0.041$), but no association between parity and the other two skeletal sites.

Table 2 Multivariate analysis of incident clinical fractures over 16 years and incident radiographic vertebral fractures over 10 years

Clinical fragility fractures ($n = 633$)	HR[1,2]	95% CI lower	95% CI upper	*p* value
Lactation	1.006	0.996	1.016	0.206
Parity	0.975	0.909	1.045	0.473
GSQ vertebral fractures (morphometric) ($n = 98$)	OR[1,2]	95% CI lower	95% CI upper	*p* value
Lactation	0.995	0.969	1.021	0.701
Parity	1.019	0.822	1.265	0.862
mABQ vertebral fractures (morphologic) ($n = 83$)	OR[1,2]	95% CI lower	95% CI upper	*p* value
Lactation	1.006	0.975	1.038	0.688
Parity	1.015	0.992	1.039	0.913

[1] Lactation: per month of lifetime breastfeeding; parity: per liveborn child

[2] List of initial covariates: age, age at first birth, age at menarche, age at menopause, total hip aBMD, BMI, total daily calcium intake, total daily vitamin D intake, education, ever fractured, ever have breast cancer, chronic obstructive pulmonary disease, diabetes, eating disorder, inflammatory bowel disease, osteoporosis, Paget's disease of bone, rheumatoid arthritis, scoliosis, uterine cancer, contraceptive use, study site, menopause, number of births, number of months breastfeed lifetime, total number of kilocalories per day, sedentary hours, ovaries removed, race/ethnicity, use of anti-resorptives, use of bisphosphonates, corticosteroid use, ovarian hormone therapy, uterus removed, weight

Discussion

In this large, multicenter, randomly recruited, population-based cohort study with the longest published period of observation for incident fragility fractures, there was no adverse association of the number of live births nor the duration of lactation with clinical osteoporotic fractures, or morphometric (GSQ) and morphologic (mABQ) vertebral fractures in older women. Lactation also showed no adverse associations with 10-year change in aBMD. Parity showed a slightly greater decline in aBMD of the femoral neck but no association with aBMD change of the total hip or lumbar spine. Importantly, there were no associations of lactation with change in aBMD of the spine, the site that undergoes the greatest changes in aBMD and microarchitecture.

Many retrospective studies have provided reassuring evidence that parity and lactation are neutral or protective against fragility fractures in the long term [1]. However, prospective data have been lacking, and we found no prior study that examined incident radiographic vertebral fractures, or a randomly selected cohort of community-dwelling women. Our prospective results agree with the majority of retrospective studies that found a neutral effect (no association) of parity and lactation with clinical fracture risk [1].

Trabecular bone loses proportionately more structure during lactation as compared to cortical bone. This is in part a consequence of the greater surface area of trabecular bone, which enables osteoclasts to resorb it more rapidly, and to differential effects that the hormonal milieu of lactation (increased parathyroid hormone-related protein and low estradiol and progesterone) may have on trabecular vs. cortical bone [1]. If the lactational decline in aBMD of the spine compromises bone strength over the long term, this should increase the risk of vertebral compression fractures. However, systematic surveillance with spine radiographs showed no association of morphometric and morphologic fractures of the thoracic and lumbar spine with parity or lactation.

We also analyzed parity and lactation for associations with change in aBMD over 10 years. Lactation was not associated with change in aBMD at any skeletal site, whereas parity showed a small association with aBMD decline in the femoral neck but not the total hip or spine. The finding in the femoral neck may be clinically unimportant and a chance result. If adjusted by the Bonferroni method for multiple comparisons because three aBMD sites were analyzed, the *p* value would no longer be significant. The lack of an association of parity with hip fractures reinforces that the change in aBMD of the femoral neck is probably a chance finding.

Compared to nulliparous women, parity can confer protective effects against fracture through several mechanisms, in particular its association with greater body weight and body mass index. Parous women are also less likely to have intervals of subfertility related to silent ovulatory disturbances within regular cycles, or lower estradiol and progesterone with oligo- or amenorrhea, which could cause low peak bone mass, or bone loss during the reproductive years [22]. These confounding effects on menstrual disturbances were controlled in our analysis by adjusting for anthropometric and reproductive characteristics in the multivariate analyses. Parity and lactation have been reported in a few clinical [23, 24] and multiple animal studies [10–12, 25, 26] to be associated with a greater cross-sectional diameter of the femur, femoral neck, or tibia. Such a change in bone geometry could develop in compensation to the increased weight bearing of pregnancy and the physiological loss of bone mass during lactation [7]. From an engineering perspective, an increased cross-sectional diameter offsets the potential decline in bone strength that would otherwise be implied by a decline in aBMD [7].

The CaM*os* cohort of ~6500 women was nominally far smaller than the WHI observational cohort of ~93,000 women, which was recently analyzed for associations of parity and lactation with skeletal outcomes [15]. However, 68.9% (4503 of 6539) of surviving CaM*os* subjects had aBMD measurements done and were observed for a longer follow-up of 10 years, as compared to only 6.2% (5919 of 93,676) of the WHI cohort, which followed women for a shorter duration of 7.8 years [15]. CaM*os* analyzed fracture outcomes for 16 years as compared to a mean of 7.8 years in WHI and accumulated 633 clinical fragility fractures as compared to 1928 in WHI.

Table 3 Multivariate linear regression analysis of decline in areal BMD at lumbar spine, total hip, and femoral hip neck over 10 years

	Beta[1,2]	95% CI lower	95% CI upper	*p* value
Lumbar spine				
Lactation	−0.0002	−0.0031	0.0028	0.919
Parity	−0.0148	−0.0401	0.0107	0.250
Total hip				
Lactation	0.0006	−0.0015	0.0027	0.562
Parity	−0.0129	−0.0302	0.0044	0.143
Femoral neck				
Lactation	−0.0007	−0.0028	0.0014	0.502
Parity	0.0189	0.0020	0.0358	0.029

[1] Beta: lactation = g/cm^2 per month of lifetime breastfeeding; parity = g/cm^2 per live child born

[2] List of initial covariates: age, age at first birth, age at menarche, age at menopause, total hip BMD, BMI, total daily calcium intake, total daily vitamin D intake, education, ever fractured, ever have breast cancer, chronic obstructive pulmonary disease, diabetes, eating disorder, inflammatory bowel disease, osteoporosis, Paget's disease of bone, rheumatoid arthritis, scoliosis, uterine cancer, contraceptive use, study site, menopause, number of births, number of months breastfeed lifetime, total number of kilocalories per day, sedentary hours, ovaries removed, race/ethnicity, use of anti-resorptives, use of bisphosphonates, corticosteroid use, ovarian hormone therapy, uterus removed, weight

Whereas the WHI analysis captured only clinical vertebral fractures, the evaluation of systematically collected spine radiographs in CaM*os* participants over age 50 enabled all incident vertebral compression fractures to be captured. Unlike the convenience cohort that comprised WHI, CaMos was a randomly recruited cohort. Both studies agree that there were largely no substantive associations of parity or lactation with clinical fracture risk, whereas WHI reported a protective effect against hip fractures that was not seen in this analysis of CaM*os* data. WHI and CaM*os* both found no consistent associations of parity or lactation with changes in aBMD.

Strengths of this study include its large size of randomly recruited, community-dwelling women; prospective nature with annual capture and verification of clinical fracture data; the use of periodic spine radiographs to capture vertebral fractures; obtaining aBMD measurements at baseline and years 5 and 10; the baseline and repeated questionnaires; and the nutritional assessments to determine intakes of calcium and vitamin D. Limitations include that few women breastfed for prolonged periods; about half fell into the category of never lactating or for at most 1 month, and the mean lifetime duration of breastfeeding was only 12 months among those who did lactate. Other limitations include that the majority of participants were Caucasian, and that self-reported durations of lactation are subject to recall bias (although a study from Norway is reassuring that women have accurate recall 20 years later [27]).

In conclusion, over 10 to 16 years of follow-up, parity and lactation each showed largely neutral associations with the risk of osteoporotic fragility fractures, morphometric or morphological vertebral fractures, and change in aBMD. These randomly obtained, population-based data provide strong reassurance that two common and positive reproductive experiences for women do not have negative long-term effects on the risks of developing fragility fractures or a more rapid decline in aBMD.

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Authors' contributions

Study design: SCH, ZG, GM, JCP, CSK. Study conduct: SCH, ZG, GM, JCP, CSK. Data collection: SCH, SMK, DG, WDL, KSD, JPB, LP, BL, JCP, CSK. Data analysis: SCH, ZG, WDL, CSK. Data interpretation: all authors. Drafting manuscript: SCH and CSK. All authors have revised the manuscript content and approved the final version. CSK takes responsibility for the integrity of the data analysis.

Compliance with ethical standards

Conflicts of interest None.

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