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The Relationship between Parity and Bone Mineral Density in Women Characterized by a Homogeneous Lifestyle and High Parity

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Context: We reported previously that Old Order Amish (OOA) women have fewer hip fractures and higher bone mineral density (BMD) than non-Amish Caucasian women.

Objective: The objective of this study was to determine whether the high parity characteristic of OOA women contributes to their relative bone health. Previous data on the long-term effects of parity on BMD have yielded conflicting results with few data from very high parity populations. This observational study included participants in the Amish Family Osteoporosis Study, begun in 1997 to identify genetic and clinical determinants of osteoporosis in the OOA. We measured BMD by dual-energy x-ray absorptiometry at the spine, hip, and distal radius in 424 parous OOA women aged 40 and older (mean age, 57.7 ± 12 yr; mean parity, 7.6 ± 2.9).

Results: Increasing parity was associated with later menopause ($P = 0.001$) and modestly, but not significantly, higher body mass index (BMI) ($P = 0.09$). Increasing parity was associated with higher BMD at the total hip and trochanter (age-adjusted $P = 0.02$ and 0.03), no longer statistically significant after accounting for BMI. Among women aged 50–59 yr, parity was strongly associated with BMD even after accounting for age and BMI (age-adjusted $P = 0.02$), although this was not true for women younger than 50 or at least 60 yr old.

Conclusions: We conclude that high parity is associated with increased hip BMD in OOA women, largely mediated by higher BMI. The parity-hip BMD association remained statistically significant after accounting for age and BMI only in women aged 50–59 yr, partially explained by a later menopausal age with high parity. The benefit of high parity on BMD appeared to be lost soon after the menopausal transition, and, therefore, these data provide evidence of neither a detrimental nor beneficial effect of high parity on long-term bone health. ***(J Clin Endocrinol Metab* 90: 4536–4541, 2005)**

WE HAVE REPORTED previously that Old Order Amish (OOA) women have a reduced incidence of hip fracture and higher bone mineral density (BMD) than non-Amish Caucasian women (1). Possible explanations for these differences may involve lifestyle differences between the Amish and non-Amish and/or differences between the populations in reproductive health characteristics. For example, a striking feature of OOA women is their relatively high parity, a characteristic that may affect the process of bone loss with age.

Pregnancy is associated with a transient decrease in bone mass (2, 3). However, reports on the long-term effects, more relevant to the risk of hip fracture, have been less consistent (4–9, 11–24). Over a lifetime, increasing parity might be expected to protect against bone loss because of pregnancy-related increases in body weight, intestinal calcium absorption and cumulative estrogen exposure, and a later age at menopause (20, 22). Indeed, several reports have shown a positive correlation between parity and BMD (19–23, 25) and a reduced hip fracture rate (26), although other studies have reported either no correlation between parity and BMD (4–9, 11–14, 24, 27) or a negative correlation (15–18). However, many studies of this issue have been performed in premenopausal women or in women younger than the age typically seen for osteoporotic fracture (3, 7, 8, 14, 19). In addition, many studies have been conducted on women with low (*e.g.* 1–3) parity (4, 6, 12, 13, 20, 24). The few studies of parity and BMD conducted in relatively high parity (more than or equal to five live births) postmenopausal women have provided conflicting results (18, 22). Additional data, particularly from very high parity populations, are needed to help clarify these discrepancies.

We hypothesized that the higher BMD in OOA women and their apparently more favorable bone health might be partially attributable to their relatively high parity. The OOA are a good population in which to study parity effects on BMD for many reasons. Multiparity is the cultural norm, and sibships of eight or more are common. Unlike many populations studied, OOA women rarely smoke or consume alcohol and have a high level of physical activity. Confounding effects of drugs are minimized in the OOA; they do not use oral contraceptives, rarely use postmenopausal estrogen, and generally avoid prescription drugs. We have evaluated our hypothesis that high parity is associated with increased BMD in a cohort of Amish women aged 40 yr and older residing in Lancaster, Pennsylvania.

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Abbreviations: AFOS, Amish Family Osteoporosis Study; BMD, bone mineral density; BMI, body mass index; OOA, Old Order Amish.

Subjects and Methods

Amish Family Osteoporosis Study

The Amish Family Osteoporosis Study (AFOS) (1, 28) was started in 1997 with the goal of identifying the genetic determinants of osteoporosis in this population. The OOA population was chosen for this study because of the availability of large extended families in a confined geographic location and our previous good working relationship with the OOA on other research studies. Individuals believed to be at risk for osteoporosis by virtue of their fracture history and/or previous bone density measurements were recruited into the study as index cases. These individuals were recruited by word-of-mouth, a community-wide mailing, advertisements in an Amish newspaper, or by referral from local physicians. BMD was measured by dual-energy x-ray absorptiometry. Individuals found to have a T score of −2.5 or less in either the hip or spine were designated as probands. We then invited the probands' spouses and all first-degree relatives aged 20 yr and over to participate in the study. Any spouse or first-degree relative having a T score of −2.5 or lower at the spine or hip on our bone densitometry test was also designated as a proband. The protocol was approved by the Institutional Review Board of the University of Maryland. Informed consent, including permission to contact relatives, was obtained before participation.

Parity study

This report is based on 424 parous women participating in the AFOS, aged 40 and older, recruited between March 1997 and September 2003. The total number of women recruited into the AFOS during this time frame aged 40 and older was 508. Sixty-four of these women were nulliparous (of whom 44 were unmarried) and were therefore excluded from these analyses. An additional 20 women were excluded because of current use of medications with potential effects on bone metabolism (10 on estrogen, seven on bisphosphonates, and three on chronic glucocorticoids), leaving a total of 424 parous women who comprise the analysis group for this study.

Amish women typically marry in their early 20s, do not practice birth control, and generally have their first child within the first few years of marriage. Divorce is not practiced. Breastfeeding is common practice. Tobacco smoking is extremely rare in OOA women, nor do Amish women typically drink alcohol. Physical activity levels in the Amish tend to be high relative to non-Amish populations. The typical daily calcium intake is 900 mg daily (1).

Study protocol

All study participants were evaluated at the Amish Research Clinic in Strasburg, PA. A medical history and physical examination were performed. Relevant to this report, the history included past medical problems, current use of prescription medications, age of menarche, and reproductive history. We defined parity as the number of live births reported by the woman, which was in excellent agreement with the Fisher Book (29), a published record of Amish genealogies. The cumulative duration of lactation was defined as the number of months the woman reported breastfeeding each child, summed across all children. Women were defined to be postmenopausal if they reported fewer than two menstrual cycles over the previous 12 months. Forty-five women reported a history of hysterectomy; of these, all were over the age of 40 and were considered for these analyses to be postmenopausal. A composite variable of cumulative estrogen exposure was defined as age at menopause minus age at menarche. Physical examination included weight in standard Amish clothing without shoes and height using a stadiometer.

BMD was measured by dual-energy x-ray absorptiometry, using a Hologic 4500W (Hologic, Bedford, MA), at the lumbar spine, hip, and forearm by a registered nurse certified in bone densitometry. The coefficient of variation, determined annually by three sequential measures on 1 d for each of 15 individuals, was 0.90% for total hip and 0.71% for the spine (L1–L4). In addition to the BMD measures, we evaluated whether parity was associated with femoral width. This analysis was motivated by the hypothesis that increasing parity, through an associated increase in body weight, might increase bone size. An increase in bone size would not be detectable by changes in BMD but could affect bone strength. Cortical width of the femur, defined as the distance from the center of the femoral head to the intersection of the neck and shaft axes, was measured by hip structural analysis, as described previously (30, 31).

Statistical analysis

We initially compared mean values of reproduction-related variables and BMD across categories of parity and then estimated the effects of parity and the reproduction-related variables on BMD while adjusting for age. Because our sample included related women within families, we conducted all analyses using a variance component modeling framework to account for the residual correlations in BMD potentially existing among related women. Briefly, this approach models the covariance between each pair of individuals within the pedigree as a function of their degree of relationship, the trait heritability (in this case, BMD), and the phenotypic variance of the trait. To evaluate the effects of parity on BMD, we compared the likelihood of the data in which we allowed for a linear effect of parity (the full, or unconstrained, model) with that of a restricted model in which the parity effect was constrained to be zero. Parameter effects were estimated conditional on the residual correlations between study subjects in BMD using maximum likelihood procedures. Significance testing was conducted using the likelihood ratio test. To determine whether observed associations between BMD and parity could be explained by reproduction-related characteristics [*e.g.* body mass index (BMI), age at menopause, and duration of lactation], we reanalyzed the data with adjustment for these variables. The variance component analyses were performed using the SOLAR software package (10).

Results

Clinical characteristics of the 424 women included in the analysis are shown in Table 1 according to parity. The number of children among these parous women ranged from 1–18 (Fig. 1), with a mean ± SD parity of 7.6 ± 2.9 live births. The mean age of parous women was 57.7 ± 12.0 yr and was not significantly correlated with parity level. Increasing parity was associated with later age at menopause ($P = 0.001$), higher cumulative estrogen exposure ($P = 0.003$), increased total duration of lactation ($P < 0.0001$), and, among postmenopausal women, fewer years since menopause ($P = 0.001$). Increasing parity was also modestly, but not significantly, associated with higher BMI ($P = 0.09$) but was not associated with age at menarche ($P = 0.89$). The Z scores for BMD at the spine and hip did not differ significantly from zero, suggesting that mean BMD at these sites was comparable with that in age-matched non-Amish Caucasian women. Increasing parity was associated with increasing Z scores for BMD at the hip ($P = 0.05$) but not at the spine ($P = 0.48$) or ultradistal radius ($P = 0.55$).

Mean levels of BMD are shown according to parity in Table 2. Increasing parity was significantly associated with increasing BMD at the total hip (age-adjusted $P = 0.02$) and trochanter (age-adjusted $P = 0.03$) but not with BMD at the spine ($P = 0.39$), femoral neck ($P = 0.20$), ultradistal radius ($P = 0.07$), or one-third radius ($P = 0.89$).

The effects of parity on BMD are shown in Table 3, with three separate sets of adjustments: one for age only; a second for age and BMI; and a third for age, BMI, and other reproduction-related variables. As indicated previously, parity was significantly associated with BMD at the total hip and trochanter, with BMD increasing on average by 0.006 g/cm^2 per child at the total hip (or 0.030 g/cm^2 per five children) and 0.004 g/cm^2 per child (or 0.020 g/cm^2 per five children) at the trochanter. When adjustment was made also for dif-

TABLE 1. Clinical characteristics of the study population according to number of children (values represent means ± SD)

Variable	No. of children 1–4 (n = 64)	5–7 (n = 149)	8–10 (n = 149)	11+ (n = 62)	Age-adjusted *P* value
No. of children[a]	3.5 ± 0.7	6.1 ± 0.8	8.9 ± 0.8	12.6 ± 1.8	
Age (yr)	57.2 ± 10.9	58.7 ± 13.1	56.3 ± 10.7	59.1 ± 12.8	0.29
BMI (kg/m^2)	27.1 ± 5.1	29.2 ± 6.3	29.6 ± 5.9	30.1 ± 6.2	0.09
Postmenopausal (%)	56.2	59.7	59.7	64.5	0.08
Age at menarche (yr)	13.4 ± 1.4	13.1 ± 1.3	13.2 ± 1.3	13.4 ± 1.4	0.89
Age at menopause (yr)[a]	45.9 ± 6.3	48.6 ± 4.1	48.9 ± 3.8	50.0 ± 4.3	0.001
Estrogen exposure[a]	32.9 ± 5.7	35.3 ± 4.1	35.7 ± 9.8	36.5 ± 4.4	0.003
Years since menopause[a]	16.8 ± 11.2	17.5 ± 10.3	13.1 ± 9.8	15.6 ± 10.6	0.001
Lactation (total months)	15.3 ± 17.0	35.3 ± 37.0	57.1 ± 49.3	76.3 ± 53.0	<0.0001
Lactation (months/child)	4.6 ± 4.8	5.7 ± 5.7	6.4 ± 5.4	6.3 ± 4.4	0.11
Spine T score	−1.58 ± 1.53	−1.36 ± 1.39	−1.52 ± 1.30	−1.54 ± 1.62	0.62
Spine Z score	−0.42 ± 1.48	−0.03 ± 1.18	−0.34 ± 1.18	−0.21 ± 1.63	0.48
Total hip T score	−0.67 ± 1.40	−0.46 ± 1.36	−0.42 ± 1.17	−0.42 ± 1.41	0.09
Total hip Z score	0.10 ± 1.32	0.52 ± 1.19	0.40 ± 1.05	0.61 ± 1.17	0.05
Ultradistal radius T score	−0.23 ± 1.02	−0.31 ± 1.22	−0.27 ± 1.46	−0.77 ± 1.47	1.00
Ultradistal radius Z score	0.78 ± 0.75	0.99 ± 0.88	0.88 ± 1.06	0.82 ± 0.96	0.55

[a] Postmenopausal women only (n = 254).

ferences in BMI, the effect of parity on BMD was substantially diminished and no longer achieved statistical significance at any site. Additional adjustment for other reproduction-related variables reduced still further the magnitude of the parity BMD association.

Because families enrolled in the AFOS were ascertained on the basis of an osteoporotic proband, we repeated our analyses on a subsample of 93 women who were enrolled into the study because they were either spouses of AFOS probands or spouses of a relative of the proband. Thus, these "married-in" women represented a more random sample of OOA women with respect to their BMD values because their recruitment was independent of their bone mass or their relatives' bone mass. The parity effect on BMD in this sample was smaller than that observed in the full sample (0.012 g/cm^2 increase in BMD per five children in the married-in sample *vs.* 0.030 g/cm^2 in the full sample) and did not achieve statistical significance.

To determine whether the correlation between parity and BMD varied according to proximity to menopause, additional analyses of parity and hip BMD were performed in women aged 40–49 yr (n = 142), 50–59 yr (n = 112), and 60 yr and older (n = 170). These age groupings were assigned to isolate the group of women undergoing the menopausal transition, occurring approximately in the sixth decade (ages 50–59 yr). As shown in Table 4, the correlation between parity and BMD was highly significant among women aged 50–59 yr (0.013 g/cm^2 per child; age-adjusted $P = 0.01$), whereas there was virtually no parity-BMD association in the younger or older age groups. The parity-BMD correlation in the 50–59 yr age group was reduced slightly after adjusting for BMI (from a 0.013 g/cm^2 increase in BMD per child to a 0.009 g/cm^2 increase in BMD per child) but still remained statistically significant ($P = 0.03$). However, the association of parity with hip BMD was substantially diminished, and no longer achieved statistical significance, when the analyses

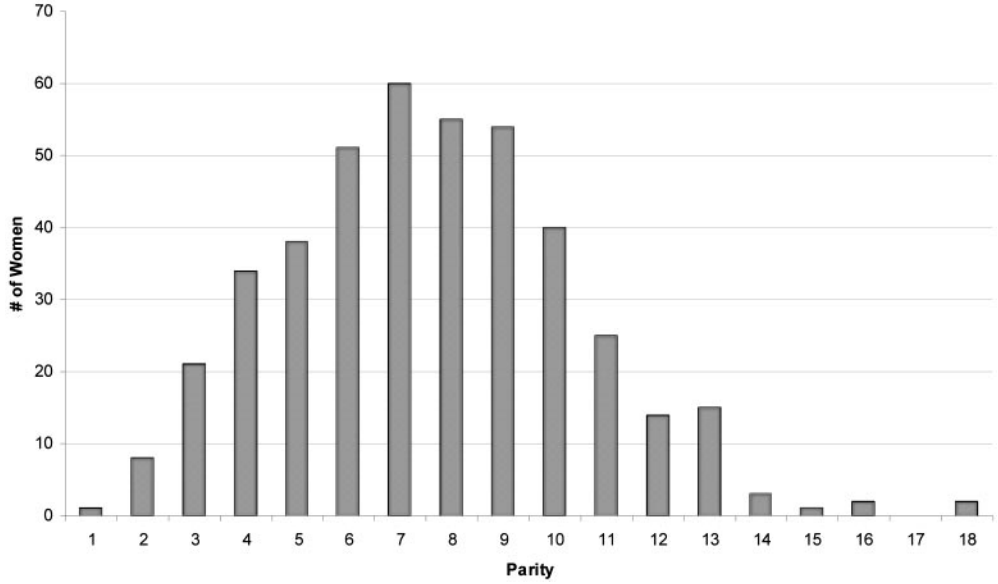

FIG. 1. Number of children among Amish women age 40 yr and older.

TABLE 2. Mean ± SD BMD for Amish women aged 40 and older according to number of children

Site	No. of children				Age-adjusted *P* value
	1–4 (n = 64)	5–7 (n = 149)	8–10 (n = 149)	11+ (n = 62)	
Spine (g/cm^2)	0.872 ± 0.172	0.891 ± 0.169	0.879 ± 0.144	0.877 ± 0.174	0.39
Total hip (g/cm^2)	0.861 ± 0.171	0.885 ± 0.169	0.892 ± 0.143	0.907 ± 0.206	0.02
Femoral neck (g/cm^2)	0.775 ± 0.149	0.793 ± 0.156	0.797 ± 0.136	0.791 ± 0.182	0.20
Trochanter (g/cm^2)	0.655 ± 0.135	0.680 ± 0.131	0.688 ± 0.118	0.685 ± 0.126	0.03
Ultradistal radius (g/cm^2)	0.442 ± 0.071	0.408 ± 0.064	0.412 ± 0.077	0.381 ± 0.074	0.07
One-third radius (g/cm^2)	0.671 ± 0.059	0.666 ± 0.071	0.668 ± 0.085	0.639 ± 0.085	0.89

were adjusted also for number of years since menopause (0.004 g/cm^2 increase in BMD per child; $P = 0.26$, adjusted for age, BMI, and menopausal status).

Analyses were also conducted in the full sample of 424 women to evaluate the relationship between parity and femur size, represented by cortical width at the narrow neck and shaft sites. These analyses revealed no association of parity with width at the narrow neck (0.001 ± 0.039 g/cm^2 increase in BMD per child; $P = 0.73$) or shaft (0.003 ± 0.033 g/cm^2 increase in BMD per child; $P = 0.45$).

Discussion

The OOA population offers numerous strengths for evaluating the relationship between parity and fracture risk. Perhaps most important of these is the very high parity characteristic of this population. The very high parity in the OOA should reveal parity-BMD associations that might not be apparent in studies of women of lower parity. Second, the OOA lifestyle tends to be very homogeneous, and many environmental exposures influencing BMD tend to occur relatively less frequently in this population. For example, OOA women rarely smoke or drink alcohol, have a high level of physical activity, and rarely use oral contraceptives or postmenopausal estrogen replacement therapy.

Our analyses revealed a positive and statistically significant correlation between increasing parity and increasing BMD at the hip but not at the spine or ultradistal radius. However, the hip correlations were markedly reduced and no longer statistically significant after adjusting for BMI, suggesting that the higher BMD observed in highly parous women may occur secondarily to parity-associated weight gain and the accompanying beneficial effects of mechanical loading on bone. Any effects of parity on BMD operating independently of BMI are likely to be small and could not be detected in our sample of more than 400 women. The lack of association found in our data between parity and spine BMD is possibly explained by a lesser effect of BMI on spine compared with hip BMD. At least some of the recent studies on parity and BMD failed to consider differences in BMI as a mediating factor (18, 22).

Our subgroup analysis revealed parity to be strongly correlated with hip BMD among women aged 50–59 yr but not in younger or older women. The parity-hip BMD correlation persisted in women aged 50–59 yr even after adjustment for age and BMI. A possible explanation for this finding is that high parity marks a delayed transition into menopause, so that highly parous women are less likely than their lower parous counterparts to have experienced the rapid bone loss that accompanies this transition. This hypothesis is, in fact, consistent with our observation that the effect of parity on hip BMD was markedly diminished when the analysis was further adjusted for the effect of age since menopause.

If the parity effect of BMD observed in women aged 50–59 yr is attributable to high parity marking a later menopause, then one might also expect to see such an association in older women. The absence of such an effect in our data are thus noteworthy, although one might speculate that a beneficial effect of parity on BMD might decline in older women because the menopausal transition has already occurred and the beneficial effect of longer estrogen exposure due to delayed menopause in high parity has waned, similar to the waning effect of exogenous estrogen on BMD after the estrogen has been discontinued. Whatever the reason, given the lack of association between hip BMD and parity in older ages, it is unlikely that the small temporary beneficial effect of parity on BMD observed in the sixth decade (BMD gain of 0.03 g/cm^2 for five-child parity difference) has any lasting influence on fracture risk in the elderly years when hip fracture typically occurs.

The association between high parity and delayed menopause may be particularly pronounced in the OOA compared with other populations because of the relatively high

TABLE 3. Effects of parity on BMD among parous women aged 40 and older (n = 424)

Site	Adjusted for age		Adjusted for age and BMI	
	Parity effect (g/cm^2) (scaled to a five-child difference in parity)	*P* value	Parity effect (g/cm^2) (scaled to a five-child difference in parity)	*P* value
Spine	0.010	0.39	0.003	0.69
Total hip	0.030	**0.02**	0.018	0.10
Hip neck	0.014	0.20	0.006	0.58
Hip trochanter	0.020	**0.03**	0.012	0.13
Arm, ultradistal	−0.014	0.07	−0.014	0.07
One-third radius	−0.001	0.89	−0.002	0.81

Bold indicates *P* values significant at ≤ 0.05.

TABLE 4. Effects of parity on total hip BMD in women aged 40–49, 50–59, and 60+ yr

Adjusted for	40–49 yr (n = 142)		50–59 yr (n = 112)		60+ yr (n = 170)	
	β	*P*	*β*	*P*	*β*	*P*
Age	0.002	0.58	0.013	0.01	0.005	0.25
Age, BMI	−0.002	0.49	0.009	0.03	0.003	0.34
Age, BMI, years since menopause	−0.002	0.45	0.004	0.26	0.003	0.35

parity and the general avoidance of birth control in this population. Our finding that the parity-hip BMD correlation was observed exclusively among 50- to 59-yr-old Amish women may to help explain some of the conflicting results of the parity-BMD relationship reported across studies. For example, in high parity populations like the OOA, the strength of the parity-BMD association will be a function of the proportion of the study population in the 50–59 yr range. In support of this concept, among studies reviewed here, several conducted on women less than 50 yr old (7, 8, 14) and on women over 70 yr old (5) found no parity-BMD correlation. Among those studies that have reported a positive association between increasing parity and increasing BMD, most (19, 21–23), but not all (20), included large significant proportions of women aged in their 50s. Thus, it is possible that some of the conflicting results reported in the literature may be attributable to differences in the ages of the populations studied.

Very few studies have evaluated the relationship between parity and BMD in postmenopausal women with very high parity (18, 22). In Hispanic women from Columbia characterized by high parity, parous women were found to have higher BMD at the hip than nulliparous women, but, among parous women, and especially those with two or more children, there was no consistent trend between number of deliveries and BMD (not adjusted for BMD) (22). This result is in contrast to our own finding of a positive correlation between parity and hip BMD (unadjusted for BMI), although the Columbian study grouped all women with five or more deliveries into a single category for analysis. The relationship between parity and BMD has also been evaluated among postmenopausal women from Turkey (18). Also in contrast to our own findings, these investigators reported an inverse correlation between parity and BMD of the hip and spine (*i.e.* increasing parity associated with decreasing BMD) (18). However, women enrolled in the Turkish study were osteoporotic, and the relationship between parity and BMD in osteoporotic populations may differ from that in nonosteoporotic populations.

A major strength of our study is the ultra high parity observed in this population, a consequence of a relative avoidance of birth control in the OOA compared with other populations and the value placed on large families. The Amish practice of avoiding alcohol and tobacco and reluctance to take prescription medication also minimizes the potential confounding effects of these variables.

An important limitation of our study is that our sample included families enriched for osteoporosis and/or low BMD. However, we also observed a very modest, albeit not statistically significant, association between increasing parity and increasing hip in our married-in subsample, a population that should be more representative of the general OOA population in terms of bone health. These results support our overall conclusion of a positive correlation between parity and BMD, although the magnitude of effect is modest and largely mediated by a parity-associated increase in BMI.

We conclude that parity is associated with increased hip BMD, although this association appears to be largely mediated by an accompanying increase in BMI seen with high parity. The one exception to this conclusion is for women aged 50–59 yr, in whom the parity-BMD correlation appears to be independent of BMI, but is possibly explained by a later menopausal age occurring with high parity. The beneficial bone mass effect of a delay in menopause is no longer significant by age 60, suggesting that the benefit of high parity on BMD may be lost soon after the menopausal transition. These data provide evidence of neither a detrimental nor beneficial effect of high parity on long-term bone health.

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