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Bonny L. Specker
South Dakota State University, Bonny.Specker@sdstate.edu

Howard E. Wey
South Dakota State University, howard.wey@sdstate.edu

Teresa L. Binkley
South Dakota State University, teresa.binkley@sdstate.edu

Tianna M. Beare
South Dakota State University, Tianna.Beare@sdstate.edu

Eric P. Smith
University of Cincinnati

See next page for additional authors

Authors
Bonny L. Specker, Howard E. Wey, Teresa L. Binkley, Tianna M. Beare, Eric P. Smith, and Frank Rauch

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Bonny L. Specker, Ph.D.[1], **Howard E. Wey, Ph.D.**[1], **Teresa L. Binkley, Ph.D.**[1], **Tianna M. Beare**, **Eric P. Smith, M.D.**[2], and **Frank Rauch, M.D.**[3]

Bonny L. Specker: bonny.specker@sdstate.edu; Howard E. Wey: howard.wey@sdstate.edu; Teresa L. Binkley: teresa.binkley@sdstate.edu; Tianna M. Beare: tianna.beare@sdstate.edu; Eric P. Smith: smithep@email.uc.edu; Frank Rauch: frauch@shriners.mcgill.ca

[1]EA Martin Program, South Dakota State University, Brookings, SD

[2]Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati College of Medicine, Cincinnati, OH

[3]Genetics Unit, Shriners Hospital for Children, Montreal, Quebec, Canada

Abstract

The relationship between aBMD and osteoarthritis (OA) remains unclear. We compared aBMD, BMC and bone size among children and grandchildren of Hutterites with hip or knee replacement (N=23 each) to children and grandchildren of age- and sex-matched controls (178 children and 267 grandchildren). There were no differences in anthropometric measures or activity levels between case and control probands, but femoral neck (FN) and spine (LS) aBMD and Z scores were greater in cases than controls (0.89 vs. 0.80 g/cm^2; 1.15 vs. 1.03 g/cm^2; 1.5 vs. 0.8; 2.4 vs. 1.2: all $p<0.05$). Hip, FN and LS aBMD (1.05 vs. 0.97, 0.92 vs. 0.84, 1.15 vs. 1.03 g/cm^2), BMC (34.1 vs. 32.0, 4.58 vs. 4.27, 69.5 vs. 62.4 g) and Z-scores (1.0 vs. 0.4; 0.9 vs. 0.2; 1.3 vs. 0.2) were greater in daughters of cases than controls (hip BMC $p=0.06$, others $p<0.05$); there were no differences between sons. Grandchildren (aged 8–39y) were categorized as growing (premenarcheal or male <14y) or not growing (≥2y post-menarcheal or males≥18y): 33 were not classified. Postmenarcheal, but not premenarcheal, granddaughters of cases had greater hip, FN and LS aBMD Z-scores (0.7 vs. −0.1; 0.6 vs. −0.1; 0.8 vs. −0.3); greater hip and spine aBMD (1.03 vs. 0.95, 1.10 vs. 0.98 g/cm^2); greater femoral neck and spine BMC (4.77 vs. 4.21, 66.7 vs. 55.4 g); and greater spine bone area (60.7 vs. 56.6 cm^2) compared to granddaughters of controls (all, $p<0.05$), which remained significant when height, weight, and age were included as covariates. Growing grandsons of cases were taller and heavier than control grandsons, and a greater hip aBMD among grandsons of cases (0.88 vs. 0.76 g/cm^2) was the only bone difference that remained significant after taking into account body size differences. Grandsons who were not growing had greater spine bone area (1.19 vs. 1.08 cm^2) if their grandparent had OA compared to grandsons whose grandparents did not have OA. We speculate that there is a genetic basis for OA that leads to early differences in growth patterns among boys and greater peak bone mass and aBMD among girls.

Corresponding Author: Bonny Specker, Ph.D., SWC Box 506, SDSU, Brookings, SD 57007, Fax: 605-688-4220, bonny.specker@sdstate.edu.

CONFLICT OF INTEREST
All authors have no conflicts of interest.

Keywords

osteoarthritis; pediatrics; genetics; estrogen; growth

INTRODUCTION

Epidemiological studies have reported an association between osteoarthritis (OA) and areal bone mineral density (aBMD), with the majority of studies finding higher aBMD in individuals with OA compared to controls [1–4]. However, some studies have found no association or an inverse association [5,6]. The etiology of this relationship remains unclear, and several hypotheses have been put forth.

One possibility is that OA is primarily a disease of bone, and that stiffer bone (higher aBMD) is less deformable, leading to increased mechanical stress on cartilage during impact loading [7]. Another possibility is that the relationship between OA and osteoporosis is an indirect one, being a result of common confounders such as body weight or activity levels. For example, greater body weight could lead to increased cartilage damage, as well as increased aBMD. However, some investigators have reported a significant relationship between OA and aBMD even after controlling for these potentials confounders [2,3].

Naganathan et al. compared aBMD in daughters of mothers with and without OA and found a higher mean aBMD in all hip regions except the trochanter in daughters of mothers with OA [8] and Jones et al. reported a greater bone size in children of individuals with OA [9]. Naganathan and coworkers speculated that high peak aBMD may be responsible, in part, for the development of OA. The daughter's mean age was 31 years and it is possible that similarities in lifestyle between the mothers and daughters could have been responsible for the observed relationships.

The Hutterites are an Anabaptist religious group who believes in isolated communal living and self-sufficiency through technologically advanced agricultural based rural lifestyle. Because they live a communal lifestyle, potential confounding factors such as access to health care, would theoretically be more similar. We are currently conducting a longitudinal study of bone health among rural populations and noted that several of the Hutterite participants had hip and knee replacements, with an underlying diagnosis of OA. The objective of the current study was to compare aBMD, BMC and bone size among participating Hutterites with and without hip and knee replacements for OA, as well as the aBMD, BMC and bone size of their children and grandchildren for whom we also had bone measurements. This would allow us to determine whether children and grandchildren of OA subjects have higher aBMD or larger bone size prior to the development of OA, which would support the theory that changes in bone precede the development of OA.

METHODS

Cases and Controls

The South Dakota Rural Bone Health Study is a longitudinal study of bone health among rural populations aged 20–66 years, of which approximately one-third of the subjects are Hutterite (N=586) [10]. In addition to SDRBHS participants, we obtained similar study measurements on an additional 402 Hutterites, 325 aged 8 to 19 years of age and 34 older than 66 years. These 988 Hutterites were all residents of one of 17 colonies located in eastern South Dakota that participated in the SDRBHS.

Study records of participating Hutterite subjects were queried to identify any individual with either a previous joint replacement at the time of enrollment or any individual having a joint replacement once they were enrolled in the study. Twenty three individuals with hip or knee replacement were identified: 10 had single knee replacements, 5 had a single hip replacement, 3 had two knees replaced, 2 had both a knee and a hip replaced, 2 had both hips and 1 knee replaced, and 1 had both knees and a hip replaced. Medical records confirming the diagnosis of OA were obtained for nineteen of the individuals with joint replacement. Among those with medical records, there were no cases of hip or knee replacement for any reason other than OA. Two of the 4 cases for whom we did not have medical records passed away prior to obtaining a medical records release; the other 2 individuals were taking prescribed medication for arthritis. The 23 study subjects came from 17 families; one family with four sibs, one family with three sibs, one family with two sibs and 14 families with one individual with a joint replacement. Sex- and age-matched Hutterite controls were obtained by identifying a study participant closest in age to the proband case who did not have a parent or grandparent in common with the case as determined by review of the Schmiedeleut Family Record.

There were a total of 178 children and 267 grandchildren who also were study participants among the 46 cases and controls. There was some overlap among children of cases and controls. There was one child whose parents were both controls; one child whose parents were both cases; and six children, all from the same family, who were both control children and control grandchildren. Of the 267 grandchilden, eight were grandchildren of two cases, 4 were grandchildren of 2 controls, and 25 were grandchildren of both a case and a control. The age range of grandchildren was large (8–30 years) and due to the influence of growth on bone, they were further categorized into growing and not growing based on menarcheal status or age (pubertal staging was not done). A female was considered as growing if she was premenarcheal, while a male was considered growing if he was aged 14 years or less. Females at least 2 years post-menarcheal and males aged 18 or older were considered not growing. There were 41 (19 male) grandchildren who could not be classified into one of these two groups and were excluded from the analyses.

Study Procedures

Anthropometric and bone measurements were obtained. Height without shoes and weight with light clothing were determined with a portable stadiometer (SECA) and digital scale (SECA, model 770). Height measurements, recorded to the nearest 0.5 cm, were taken in duplicate and repeated if they differed by more than 0.5 cm. Weight was recorded to the nearest 0.1 kg. Z scores for height and weight were obtained using EpiInfo [11] for individuals less than 18 years of age. We also calculated sex-specific means and standard deviations from the larger cohort of Hutterites and non-Hutterites aged 18–85 years and older (571 males, 772 females) in order to obtain Z-scores for weight and height: weight (mean ± standard deviation of 74.1 ± 16 and 93.0 ± 17 kg for women and men) and height (162.8 ± 5.9 and 177.7 ± 7.0 cm for women and men).

Bone measurements of the spine and hip were measured using a Hologic QDR 4500A (Bedford, MA). Hip scans were done on the left side or the unaffected (no joint replacement) hip. Two cases and two controls did not have hip scans and two cases and two controls did not have spine scans. The coefficients of variation (CV) for spine and hip aBMD measured by QDR4500A in adults are less than 1%. Z scores for hip, femoral neck and spine bone density were obtained from the manufacturers' software (Version 12.3).

Physical activity and menarcheal age were obtained by interview. Physical activity was measured using a Seven Day Physical Activity Recall [12], which requires the participant to determine the average amount of time spent per day sleeping, sitting, or in vigorous or moderate activity during the previous week. The remaining time was classified as light activity. Vigorous

activity was considered as any activity that leads to an increase in heart rate or heavy breathing and included such activities as running, brisk walking, shoveling, etc. Moderate activity was considered as an activity that required significant movement but did not noticeably increase heart rate or result in heavy breathing. Activity patterns for both weekdays and weekend days were included and the number of days per week considered weekend days also was obtained. The average daily percent of time spent in moderate plus vigorous activity was then calculated.

Written informed consent was obtained from all participants and their parent if they were younger than 18 years. The study was approved by South Dakota State University Institutional Review Board.

Statistical Analysis

Comparisons between proband cases and controls were done using Student's t-test, chi-square, and analysis of covariance. Analyses for children and grandchildren were stratified by sex and comparison of bone outcomes was done with and without adjusting for age, height, and weight. In the instances where there were grandchildren of two cases (N=8) or two controls (N=4, growth status classified in 3), analyses were completed including the grandchild in the dataset only once. In the 25 instances (growth status classified in 20) where the grandchild was both a grandchild of a control and a case, the grandchild was only included as a grandchild of the case.

RESULTS

As expected based on the selection of controls, the sex distribution and mean ages were similar among cases and controls (Table 1). There were no differences between proband cases and controls in weight, height, BMI, or activity levels; among females the age at menarche and menopause were similar. Femoral neck and spine aBMD (Table 1) and Z scores (Figure 1) were greater in cases compared to controls. Spine ($p=0.02$), but not femoral neck ($p=0.06$), aBMD remained significantly greater when age, sex, height and weight were included as covariates.

The children of cases and controls had a mean age of 36 years and anthropometric measurements and activity levels were similar between cases and controls for both sons and daughters (Table 2 & Table 3). There was no difference in the sex distribution between cases and controls ($p=0.07$), and no differences between sons of cases and controls in any bone measure (Table 2). Daughters of cases had greater aBMD Z scores and aBMD at the total hip, femoral neck and spine, and greater femoral neck and spine BMC than daughters of controls (Table 3, Figure 2–Figure 4); these differences remained significantly different when age, weight and height were included in the statistical models.

Grandchildren of the cases and controls had an average age of 15 years and because of the large age range (8 to 30 years), and the influence of growth on bone outcomes, we categorized the grandchildren as either growing (premenarcheal females or males less than 14 years of age) or not growing (females at least 2 years post-menarcheal or males aged 18 years or older). There were 35 grandchildren who were neither classified as growing or not growing (females < 2 years postmenarcheal or males 15–17 years of age). There were no differences in the distribution of males and females between grandchildren of cases and controls who were still growing ($p=0.58$) or those who were no longer growing ($p=0.32$).

Grandsons of cases who were still growing were of similar age, yet were heavier, taller, and had greater BMIs and age- and sex-specific hip and femoral neck aBMD Z-scores than growing grandsons of controls (Table 2, Figure 2–Figure 3). Growing grandsons of cases had greater hip, femoral neck and spine aBMD, BMC and bone area than growing control grandsons when

just age was included in the analysis. However, when weight and height were included, only hip aBMD was greater in growing grandsons of cases than in controls, suggesting that bone differences at the femoral neck and spine were due to body size differences. There were no anthropometric differences between grandsons of cases and controls who were not growing (Table 2), yet spine aBMD was slightly greater in grandsons of cases than in controls even after controlling for age, weight and height (p=0.03).

Granddaughters of cases who were still growing had similar age, weight, and BMI, but were slightly taller compared to granddaughters of controls (Table 3). However, height Z scores were similar and differences in mean heights did not remain significant when age was included in the analyses indicating that height differences were due to the small age differences between the two groups. Growing granddaughters of cases had greater femoral neck and spine BMC and bone area than granddaughters of controls, but the majority of these differences were no longer significant when age, weight, and height were included in the analysis. Only a greater spine bone area among growing granddaughters of cases compared to controls remained significant when covariates were taken into account in the analysis (p=0.01)(Table 3). Granddaughters who were not growing were slightly heavier and taller, had less time in moderate plus vigorous activity, had lower grip strength, and had higher hip, femoral neck and spine aBMD Z-scores if their grandparent was a case than if their grandparent was a control (Figure 2–Figure 4, Table 3). Hip and spine aBMD, femoral neck and spine BMC, and spine bone area among granddaughters of cases remained significantly greater than granddaughters of controls after including covariates.

Similar results were obtained if the cases without medical confirmation of OA and their matched controls, as well as their children and grandchildren, were omitted from the above analyses.

DISCUSSION

We are unaware of any study that has investigated differences in aBMD Z scores and anthropometric measurements among grandchildren of individuals with history of hip or knee replacement. We observed greater aBMD, which remained statistically significant after adjusting for age, weight, and height at some bone sites among grandchildren who were no longer growing if their grandparent had a hip or knee replacements compared to grandchildren of grandparents without a hip or knee replacement. These aBMD differences were not apparent among younger grandchildren who were still growing.

Our finding of higher aBMD among daughters of individuals with joint replacements is consistent with the study by Naganathan and coworkers who found higher mean hip and femoral aBMD in 60 daughters of women with hand OA compared to daughters of women without OA (mean age of 34 y) [8]. In this study, 124 women aged 50 to 75 years were randomly selected from a defined population (North Sydney Health Area) and were invited to take part in a study of osteoporosis and OA. The daughters of these women also were invited to participate. Naganathan and coworkers found no difference in age, height, weight or any bone measure among women with and without hand OA. Among the 60 daughters (66% response rate) who took part in the study, there were no differences in age or weight between daughters of OA cases and controls, but the daughters of cases were significantly taller than daughters of controls. Adjusting for BMI, the authors found significantly greater hip and femoral neck aBMD among daughters of cases compared to controls, consistent with our findings. They did not, however, observe a greater spine aBMD in the daughters of cases as we did. Naganathan et al. speculated that greater peak aBMD may be associated with increased risk of developing OA later in life. It is possible that shared environmental influences may be responsible for the observed relationships since activity levels and obesity are likely to be more similar within a

family than between families. Due to their communal lifestyle, there should be greater similarity in environmental influences on bone between Hutterite families than between non-Hutterite families.

The cases in a population-based case-control study by Jones et al. were individuals who had undergone knee replacement for primary OA at any hospital in the capital city of Southern Tasmania (Australia) between 1996 and 2000. The controls were randomly selected individuals from Southern Tasmania who had no personal or family history of knee osteoarthritis. The offspring had a mean age of 45 years, which is slightly older than the children of our cases. Jones et al. reported greater weight, BMI and knee pain, and lower strength measures among the 188 children of OA cases compared to controls. They also investigated cartilage volume and medial tibial bone area in these offspring and found similar cartilage volume, but larger tibial bone area among the daughters of individuals with knee replacements. We did not observe a greater body size among the children of our cases compared to controls as Jones et al. reported [9], but we did find that differences in bone measures were limited to the daughters and older granddaughters with few differences among the grandsons. Jones et al. also reported sex differences, with daughters of cases having larger medial tibial bone area than controls.

The finding of lower strength measures among the older granddaughters of individuals with joint replacement is consistent with Jones et al. findings of decreased strength among offspring of cases with knee replacements. Defects in cartilage volume are considered important in the development of OA. Activity levels and strength measurements have all been shown to be positively correlated with cartilage volume in children aged 9 to 18 years [13]. Even after adjusting for activity and strength differences, boys had greater cartilage volume than girls. We found lower activity levels and strength measures among the older granddaughters of cases compared to controls, which theoretically should lead to decreased cartilage volume. Despite the lower activity levels and strength measures, which are typically associated with decreased aBMD, we still observed a greater aBMD among the granddaughters of cases compared to the granddaughters of controls.

The results of the current study support the speculation that higher aBMD observed in individuals with OA may be due to genetic factors that lead to early rapid growth among boys and higher peak bone mass among girls. Not only were bone differences observed in children, but also grandchildren of individuals with history of joint replacement from OA. One may expect that observed bone differences between children of cases and controls would be stronger than bone differences between grandchildren if genetic factors leading to high aBMD were a factor in the pathogenesis of OA. However, bone differences between grandchildren may be more apparent than differences among children due to a longer period of time that environmental exposures may influence bone in the children compared to the grandchildren.

Osteoarthritis in older individuals affects women 2–3 times more often than it affects men and our findings among sons and grandsons were markedly different than the findings among daughters and granddaughters. We found that the growing grandsons of cases were taller and heavier than grandsons of controls with a greater hip aBMD that remained significant even after taking into account body size differences. It is interesting to note that there were no body size differences between grandsons of cases and controls who were no longer growing or between the sons. We speculate based on these results that an increased growth rate early in life, or a gene or combination of genes common to both early growth velocity and OA among males may be associated with joint replacement as an older adult. There are several genes that are reported to be associated with both growth and OA. Associations between OA and IGF-1 genotype have been previously reported [14], as well as associations with procollagen type II (COL2A1) and the vitamin D receptor gene (VDR) [15–17]. However, the influence of some of these genes, at least the IGF-1 gene, on OA have not been found to be sex-specific [15].

Our findings of higher hip, femoral neck, and spine aBMD Z scores among daughters and post-menarcheal granddaughters of subjects with joint replacement are consistent with sex-specific differences in aBMD among individuals with OA and their offspring. Even controlling for covariates, significant differences in the majority of bone measures of granddaughters who were no longer growing were observed and were similar to those differences seen in the daughters. The observation that bone differences were apparent in granddaughters who were at least two years post-menarcheal, but not in premenarcheal granddaughters, suggests a possible role of estrogen in the pathogenesis of high aBMD and OA.

The preponderance of OA among women and the development of OA symptoms around the time of menopause have lead to the speculation, as early as the 1920's, that OA was a hormonally mediated disease [18]. Results from observational cohort studies are inconsistent, with some investigators finding estrogen use to protect against OA, while others find no relationship [1,19]. Randomized trials of estrogen therapy and OA have been completed, but the results are inconclusive [20,21]. Estrogen receptors (ER-alpha and ER-beta) are expressed in both chrondrocytes and bone and polymorphisms in the ERs have been shown to be associated with OA [22,23]. Bergink and coworkers suggested that there may be a greater sensitivity of ER-alpha haplotype allele PX individuals to estrogen compared with those without the PX allele [23]. This increased sensitivity may lead to increased stimulation of local bone formation and greater susceptibility to osteophyte formation, thereby explaining the association with both OA and high aBMD. The findings of high aBMD among the daughters and postmenarcheal granddaughters of individuals with hip or knee replacements is consistent with the speculation of Bergink and coworkers.

There are several limitations to the current study. First, we defined our cases on the history of joint replacement. The diagnosis of OA was confirmed by obtaining medical records for the majority of cases (83%) and omitting the cases without confirmed OA, along with their matched controls, and their children and grandchildren, did not change the results. The presence of OA, however, was not ruled out in the controls. Since access to healthcare is uniform in this population it is assumed that individuals with joint replacement had severe OA, whereas the controls, even if they had OA, were less severe cases. If some of the controls actually had OA we would expect their aBMD, and that of their children and grandchildren, to be more similar to cases. Second, the data are cross-sectional and we did not compare growth velocities of grandchildren of cases and controls. Obtaining longitudinal growth and bone measures on this cohort will provide us with the data to determine whether longitudinal changes are different between grandchildren of cases and controls. Although we had sufficient power to detect numerous differences between children and grandchildren of cases and controls, it is possible that we did not have sufficient sample size to detect other differences that may exist. Selection bias is often a problem in retrospective case-control studies when the controls are not from the same population as the cases. In the current analyses, the controls came from the same Hutterite colonies as the cases; the only difference was that they had not had a joint replacement. Due to the communal way of life, access to medical care is similar among all Hutterites, so there should not be a bias in who is receiving needed joint replacements and who is not.

In summary, we observed differences in growth parameters and bone measurements in children and grandchildren of individuals with joint replacement compared to children and grandchildren of sex- and age-matched controls. Body size differences were apparent among growing grandsons, while post-menarcheal bone differences among granddaughters and daughters were observed. These findings support a genetic basis for OA that leads to early differences in growth patterns among boys and greater bone mass and aBMD among girls.

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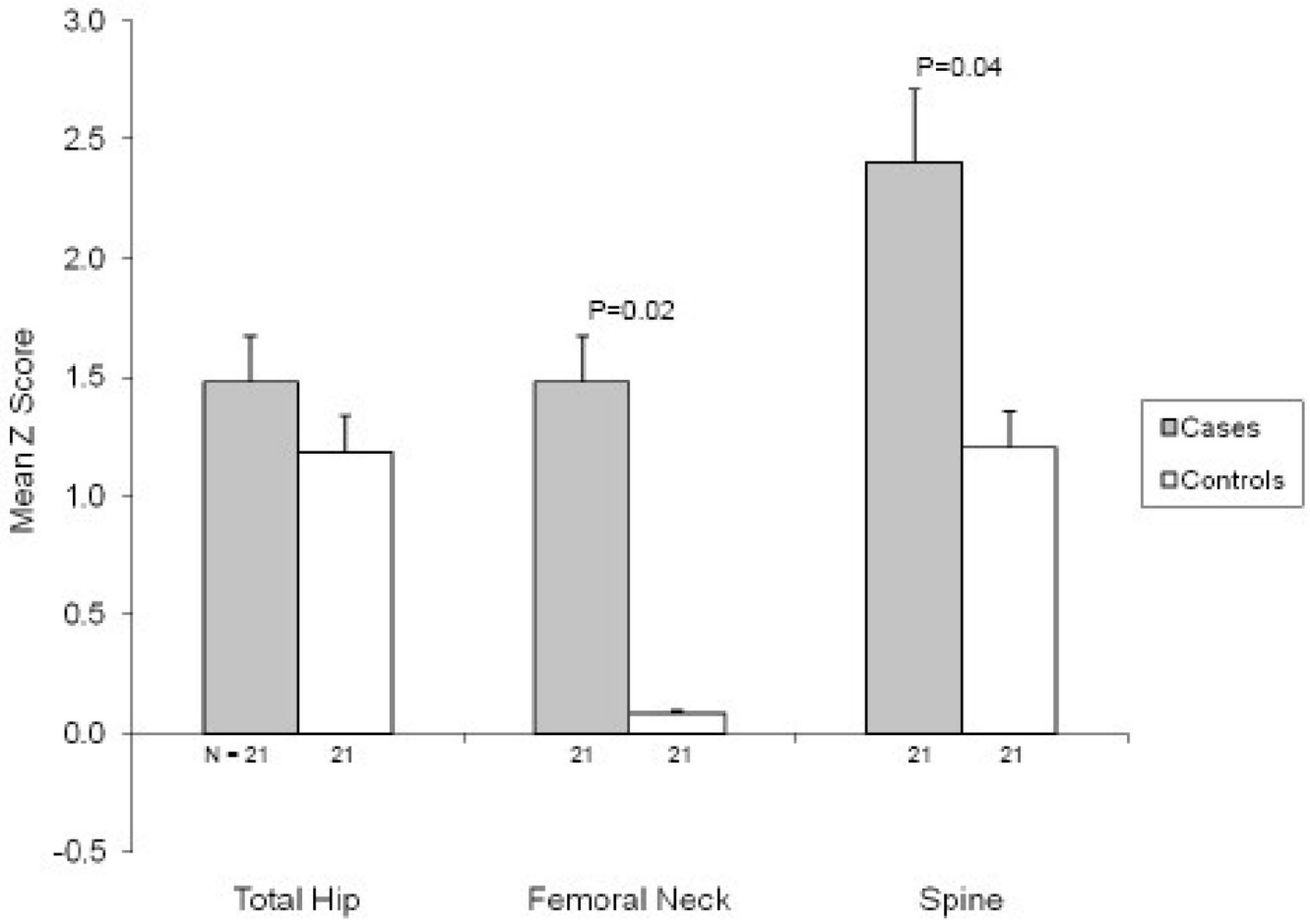

Figure 1.
Mean hip, femoral neck, and spine aBMD Z-scores of Hutterites with history of hip or knee replacement and sex- and age-matched controls. Cases had significantly greater BMD Z-scores than controls at the femoral neck and spine.

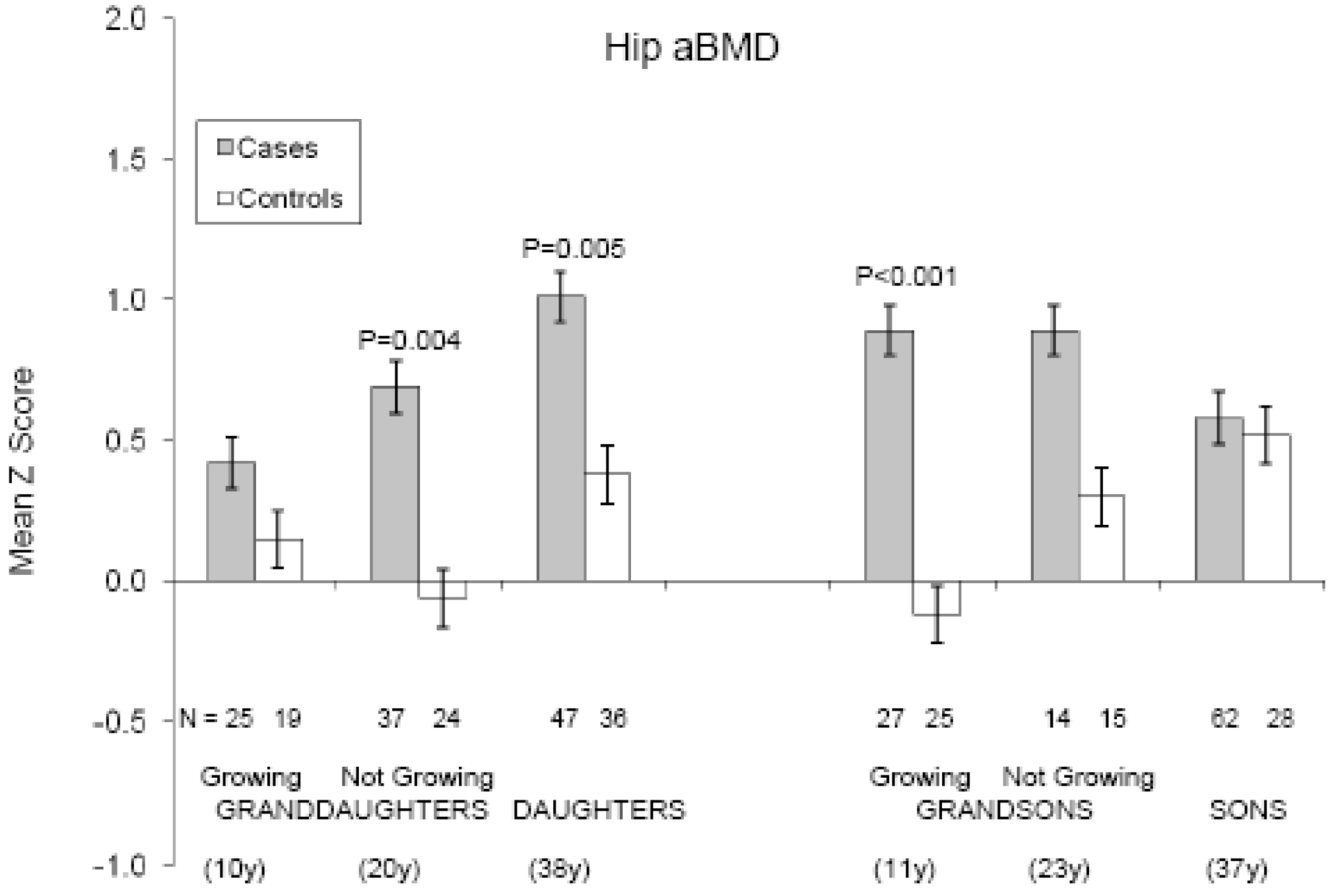

Figure 2.
Mean hip aBMD Z-scores of children and grandchildren of individuals with history of hip or knee replacement. Mean age is given in parentheses.

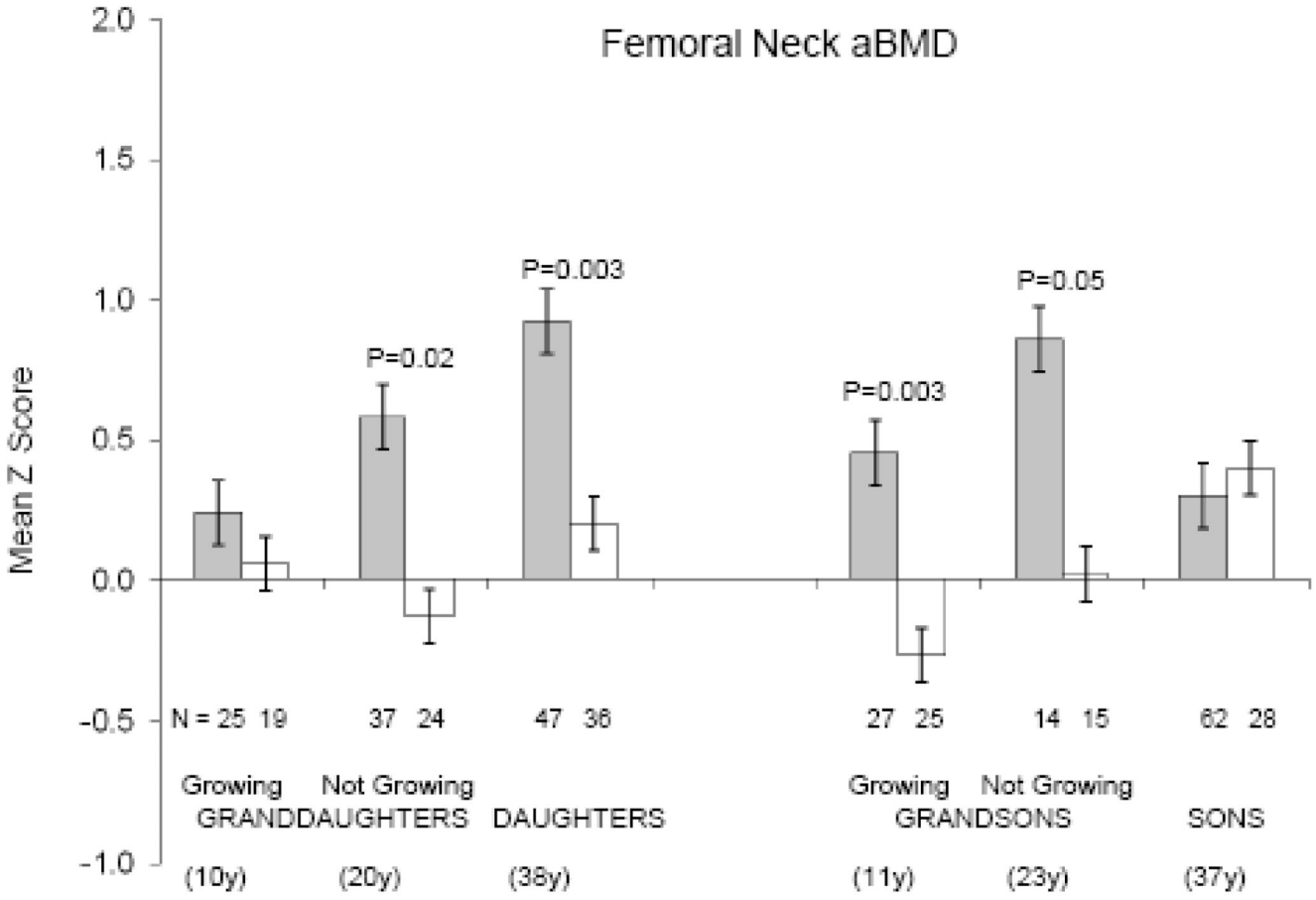

Figure 3.
Mean femoral neck aBMD Z-scores of children and grandchildren of individuals with history of hip or knee replacement. Mean age is given in parentheses.

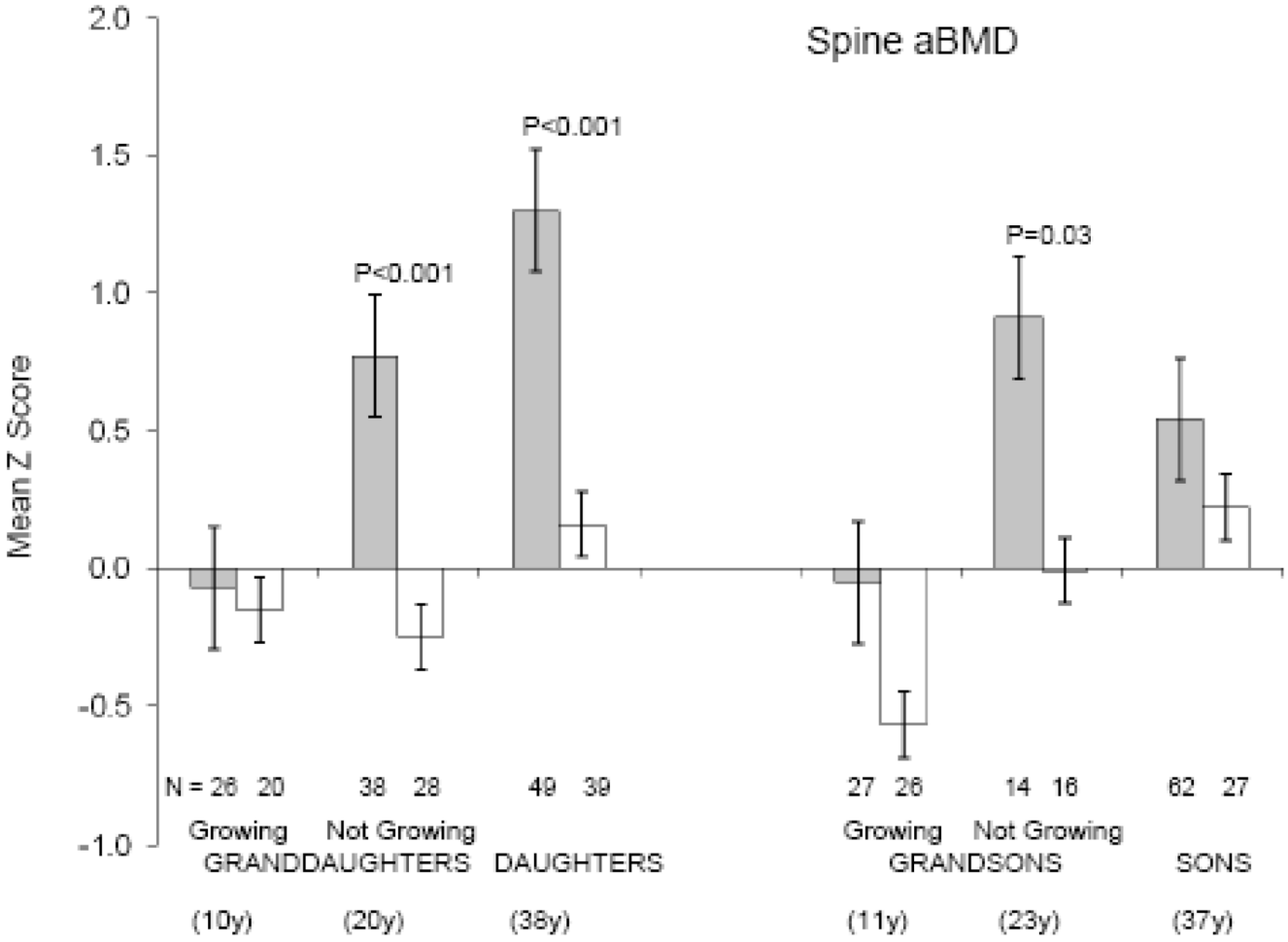

Figure 4.
Mean spine aBMD Z-scores of children and grandchildren of individuals with history of hip or knee replacement. Mean age is given in parentheses.

Table 1

Anthropometric and Bone Measurements of Probands.

	Cases	Control	Significance[a]
# Male/Female	7/16	7/16	0.99
# Married or Widowed (Male/Female)	7/13	7/16	0.10
# of Children (range) [b]	7.0 (0–13)	8.1 (0–16)	0.36
Age (y) [range]	65.5 ± 1.9 [49–77]	65.3 ± 1.9 [48–79]	0.95
Age at Menarche (y)	13.5 ± 0.4	13.4 ± 0.4	0.88
Age at Menopause (y)	41.4 ± 1.5	45.5 ± 1.6	0.06
% Time in Mod+Vig Activity [a]	12 ± 2	16 ± 2	0.16
Grip Strength (kg) [a]	30 ± 2	30 ± 2	0.70
Anthropometric Measures			
Weight (kg) [a]	88.8 ± 3.6	85.3 ± 3.6	0.43
Weight Z-score	0.5 ± 0.2	0.3 ± 0.2	0.43
Height (cm) [a]	163.1 ± 2.0	163.2 ± 2.0	0.95
Height Z-score	−0.7 ± 0.2	−0.7 ± 0.2	0.95
BMI (kg/m^2) [a]	33 ± 1	32 ± 1	0.47
Bone Measures[a]			
aBMD (g/cm^2)			
Total Hip	1.03 ± 0.03	0.98 ± 0.03	0.21
Femoral Neck	**0.89 ± 0.03**	**0.80 ± 0.03**	**0.03**
Spine	**1.15 ± 0.05**	**1.03 ± 0.05**	**0.05**
BMC (g)			
Total Hip	41.7 ± 2.5	38.0 ± 2.5	0.18
Femoral Neck	**4.81 ± 0.21**	**4.32 ± 0.20**	**0.05**
Spine	72.3 ± 4.7	64.5 ± 4.7	0.13
Bone Area (cm^2)			
Total Hip	39.6 ± 1.5	38.6 ± 1.5	0.73
Femoral Neck	5.40 ± 0.11	5.41 ± 0.11	0.64
Spine	61.9 ± 2.0	61.7 ± 2.0	0.76

Data are means ± sem.

[a] Significance when sex was included in the statistical model using analysis of covariance.

[b] Married or widowed only.

Table 2

Anthropometric and Bone Measurements of Grandsons and Sons of Probands.

	Grandsons								
	Growing			Not Growing			Sons		
	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P
Number	26	27		16	14		28	62	
Age (y) [range]	11.3 ± 0.4 [8 – 14.7]	10.6 ± 0.3 [8 – 14.9]	0.20	22.8 ± 0.9 [18 – 30]	22.0 ± 0.9 [18 – 29]	0.53	36.8 ± 1.5 [17 – 54]	35.6 ± 1.0 [19 – 50]	0.50
Weight (kg)	**48.7 ± 2.5**	**35.7 ± 2.4**	**<0.001** *a*	81.6 ± 2.3	79.0 ± 2.4	0.44	93.3 ± 3.1	90.6 ± 2.1	0.48
Weight Z-score	**0.7 ± 0.2**	**−0.1 ± 0.2**	**<0.001**	−0.7 ± 0.1	−0.8 ± 0.1	0.44	0.1 ± 0.2	−0.1 ± 0.1	0.30
Height (cm)	**150.9 ± 2.2**	**140.8 ± 2.1**	**0.002** *a*	176.2 ± 1.3	177.2 ± 1.4	0.57	178.8 ± 1.1	178.1 ± 0.8	0.60
Height Z-score	**1.0 ± 0.2**	**0.0 ± 0.2**	**<0.001**	−0.2 ± 0.2	−0.1 ± 0.2	0.57	0.1 ± 0.2	0.1 ± 0.1	0.73
BMI (kg/m^2)	**21 ± 1**	**18 ± 1**	**0.002** *a*	26 ± 1	25 ± 1	0.21	29 ± 1	29 ± 1	0.57
% in Mod+Vig Activity	16 ± 3	17 ± 2	0.73	33 ± 1	32 ± 2	0.65	25 ± 2	26 ± 1	0.82
Grip Strength (kg)	27 ± 2	23 ± 2	0.10	56 ± 2	60 ± 2	0.31	57 ± 2	56 ± 1	0.79
aBMD (g/cm^2)									
Total Hip	**0.88 ± 0.02**	**0.76 ± 0.02**	**<0.001** *a,b*	1.18 ± 0.03	1.13 ± 0.03	0.32	1.10 ± 0.03	1.09 ± 0.02	0.82
Femoral Neck	**0.80 ± 0.02**	**0.71 ± 0.02**	**<0.001** *a*	1.06 ± 0.04	0.98 ± 0.04	0.13	0.92 ± 0.03	0.94 ± 0.02	0.41
Spine	**0.72 ± 0.02**	**0.64 ± 0.02**	**0.01** *a*	**1.19 ± 0.03**	**1.08 ± 0.03**	**0.02** *a,b*	1.14 ± 0.03	1.11 ± 0.02	0.41
BMC (g)									
Total Hip	**24.8 ± 1.3**	**18.2 ± 1.3**	**<0.001** *a*	50.6 ± 2.3	50.9 ± 2.3	0.92	49.7 ± 1.6	48.8 ± 1.1	0.64
Femoral Neck	**3.84 ± 0.13**	**3.16 ± 0.13**	**<0.001** *a*	6.02 ± 0.20	5.68 ± 0.21	0.26	5.35 ± 0.16	5.54 ± 0.11	0.31
Spine	**34.5 ± 1.7**	**26.4 ± 1.7**	**0.002** *a*	81.4 ± 2.9	74.9 ± 3.1	0.14	80.5 ± 2.9	77.6 ± 1.9	0.41
Bone Area (cm^2)									
Total Hip	**27.7 ± 1.1**	**24.0 ± 1.0**	**0.02** *a*	42.9 ± 1.1	44.8 ± 1.1	0.23	45.0 ± 0.8	44.6 ± 0.5	0.67
Femoral Neck	**4.76 ± 0.09**	**4.44 ± 0.09**	**0.02** *a*	5.71 ± 0.08	5.81 ± 0.08	0.35	5.84 ± 0.07	5.90 ± 0.05	0.53
Spine	**47.0 ± 1.2**	**41.4 ± 1.1**	**0.001** *a*	68.6 ± 1.5	69.1 ± 1.7	0.82	70.4 ± 1.3	70.0 ± 0.8	0.98

Data are means ± sem. P values shown are from Student's t-test.

[a] Remained significant when age was included in the statistical model using analysis of covariance. All of the above variables were tested except age and Z-scores.

[b] Remained significant when age, weight, and height were included in the statistical model using analysis of covariance. All of the above variables were tested except age, weight, height and Z-scores.

Table 3

Anthropometric and Bone Measurements of Granddaughters and Daughters of Probands.

	Grandsons								
	Growing			Not Growing			Daughters		
	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P
Number	20	26		28	38		39	49	
Age (y) [range]	10.3 ± 0.3 [8 – 12]	9.9 ± 0.2 [8 – 12]	0.24	20.3 ± 0.7 [13 – 29]	18.9 ± 0.6 [14– 28]	0.12	36.8 1.8 [16 – 52]	36.0 ± 1.6 [14 – 55]	0.73
Weight (kg)	36.2 ± 1.9	34.1 ± 1.7	0.41	**65.6 ± 1.8**	**60.2 ± 1.6**	**0.03** ***a***	75.3 ± 2.0	71.7 ± 1.8	0.18
Weight Z-score	0.3 ± 0.2	−0.1 ± 0.2	0.15	−0.3 ± 0.1	−0.5 ± 0.1	0.11	0.1 ± 0.1	0.0 ± 0.1	0.38
Height (cm)	**142.8 ± 2.0**	**137.2 ± 1.8**	**0.05**	**163.6 ± 0.8**	**161.5 ± 0.7**	**0.04**	162.7 ± 0.8	162.6 ± 0.9	0.92
Height Z-score	0.2 ± 0.2	0.0 ± 0.2	0.54	0.3 ± 0.2	0.1 ± 0.1	0.26	0.0 ± 0.2	0.0 ± 0.1	0.99
BMI (kg/m^2)	18 ± 1	18 ± 1	0.76	24 ± 1	23 ± 1	0.11	29 ± 1	27 ± 1	0.22
% Mod+Vig Activity	16 ± 2	18 ± 2	0.55	**15 ± 2**	**23 ± 2**	**0.005** ***a,b***	23 ± 2	20 ± 2	0.26
Grip Strength (kg)	19 ± 1	18 ± 1	0.43	**30 ± 1**	**35 ± 1**	**0.005** ***a,b***	32 ± 2	33 ± 1	0.38
aBMD (g/cm^2)									
Total Hip	0.76 ± 0.02	0.71 ± 0.02	0.09	**1.03 ± 0.02**	**0.95 ± 0.02**	**0.003** ***a,b***	**1.04 ± 0.02**	**0.97 ± 0.02**	**0.005** ***a,b***
Femoral Neck	0.70 ± 0.02	0.67 ± 0.01	0.23	**0.93 ± 0.02**	**0.86 ± 0.02**	**0.02** ***a***	**0.92 ± 0.02**	**0.84 ± 0.02**	**0.005** ***a,b***
Spine	0.67 ± 0.02	0.65 ± 0.02	0.46	**1.10 ± 0.02**	**0.98 ± 0.02**	**<0.001** ***a,b***	**1.15 ± 0.02**	**1.03 ± 0.02**	**<0.001** ***a,b***
BMC (g)									
Total Hip	18.0 ± 0.9	16.2 ± 0.8	0.13	**34.5 ± 0.9**	**31.1 ± 0.8**	**0.007** ***a***	34.1 ± 0.8	32.0 ± 0.7	0.06
Femoral Neck	**3.04 ± 0.12**	**2.73 ± 0.10**	**0.05**	**4.77 ± 0.11**	**4.21 ± 0.09**	**<0.001** ***a,b***	**4.58 ± 0.10**	**4.27 ± 0.09**	**0.03** ***a,b***
Spine	**29.4 ± 1.4**	**25.2 ± 1.2**	**0.03**	**66.7 ± 1.6**	**55.4 ± 1.4**	**<0.001** ***a,b***	**69.5 ± 1.5**	**62.4 ± 1.4**	**<0.001** ***a,b***
Bone Area (cm^2)									
Total Hip	23.5 ± 0.8	22.6 ± 0.7	0.38	33.3 ± 0.5	32.6 ± 0.4	0.30	32.7 ± 0.6	33.2 ± 0.5	0.46
Femoral Neck	**4.31 ± 0.09**	**4.05 ± 0.08**	**0.04**	**5.15 ± 0.07**	**4.94 ± 0.06**	**0.02** ***a***	4.99 ± 0.06	5.09 ± 0.05	0.20

	Grandsons								
	Growing			Not Growing			Daughters		
	Cases	**Controls**	**P**	**Cases**	**Controls**	**P**	**Cases**	**Controls**	**P**
Spine	**43.1 ± 1.0**	**38.5 ± 0.9**	**0.003** ***a,b***	**60.7 ± 0.9**	**56.6 ± 0.8**	**0.001** ***a,b***	60.1 ± 0.8	60.7 ± 0.8	0.58

Data are means ± sem. P values shown are from Student's t-test.

[a]Remained significant when age was included in the statistical model using analysis of covariance. All of the above variables were tested except age and Z-scores.

[b]Remained significant when age, weight, and height were included in the statistical model using analysis of covariance. All of the above variables were tested except age, weight, height and Z-scores.