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The Association of Self-Reported Birth Weight with Bone Mineral Content and Bone Mineral Density among College-Aged Women

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THE ASSOCIATION OF SELF-REPORTED BIRTH WEIGHT WITH BONE
MINERAL CONTENT AND
BONE MINERAL DENSITY AMONG COLLEGE-AGED WOMEN

A Thesis Presented

By

VALERIE M. HASTINGS

Submitted to the Graduate School
of the University of Massachusetts Amherst
in partial fulfillment of the requirements for the degree of

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DEDICATION

To my family

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ABSTRACT

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MAY 2009

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Early life factors such as birth weight have been associated with the risk of disease in adulthood, including osteoporosis. In the United States, an estimated eight million women have osteoporosis, a disease characterized by low bone mass and associated with increased risk of fracture. Peak bone mass, achieved during early adulthood, is a key determinant of risk of subsequent osteoporosis. Prior studies have suggested that an individual's birth weight is positively associated with bone mineral content (BMC) and bone mineral density (BMD) but results have differed depending on site of bone measurement and other factors considered. We assessed the relationship between birth weight and BMC and BMD using data from the University of Massachusetts Vitamin D Status Study, a cross-sectional study of 186 US women aged 18 to 30 years. Birth weight was assessed via self report and BMC and BMD were measured by dual energy x-ray absorptiometry (DXA). Multivariable linear regression and multivariable logistic regression were used to model the association between birth weight and BMC and BMD, adjusting for established risk factors for low bone density.

After controlling for important factors, birth weight was positively associated with BMC and BMD, in large part due to the strong relationship between birth weight and body size. A better understanding of the physiology of the association between birth weight and adult body size and peak bone mass is needed to determine if birth weight is independently associated with peak bone mass.

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CHAPTER I

INTRODUCTION

Early life factors have been associated with risk of developing disease later in life. The “Barker Hypothesis” proposes that adverse influences in early life can result in permanent changes in physiology and metabolism that in turn increase disease risk in adulthood.(1)The most widely accepted explanation is programming, where a stimulus during a sensitive or critical period has irreversible long-term effects on development (2). Possible programming influences include altered fetal nutrition and exposure to excess glucocorticosteroids. Birth weight is a common measure of early life factors and low birth weight has been associated with later life conditions, including osteoporosis (3). Osteoporosis is a disease characterized by low bone mass and structural deterioration of the bone, leading to bone fragility and increased risk of fracture (4). In the United States (US), it is estimated that 10 million people have osteoporosis and nearly 34 million more are at increased risk due to low bone mass (4). Of those estimated to have osteoporosis, 80% are women and 20% are men (5). Risk of developing osteoporosis increases with age, and women can lose up to 20 % of their bone mass in the five to seven years after menopause, increasing their susceptibility to fracture (5). Osteoporosis is associated with high morbidity and low quality of life, particularly when it leads to fracture. It is not likely to cause death; however, mortality rates do appear to increase after fracture among older adults (4). Osteoporosis-related fractures cost an estimated \$19 billion in 2005 and are predicted to cost \$25.3 billion in 2025 (5).

Peak bone mass is an important determinant of the risk of developing osteoporosis. Attaining a high peak bone mass, as well as having a slow decline in bone

mass, is key to lowering risk of osteoporosis and so preventative strategies may therefore include measures to maximize peak bone mass (6). Both genetic and environmental factors contribute to peak bone mass, which is generally attained by the third decade of life (7). While a clinically relevant change in peak bone mass for the reduction in risk of osteoporosis and fracture has not been quantified, even a small increase in peak bone mass is associated with a reduction in risk (6).

Bone mass is typically measured as bone mineral content (BMC) and bone mineral density (BMD). Bone mineral content is a measure of the mass of bone, comprised of mostly calcium plus other minerals such as phosphorous, magnesium, and potassium (8). Bone mineral density is a proxy for strength of bone and attempts to measure the mass per volume (e.g. density) of bone by dividing BMC by bone area. In practice BMD is usually measured as mass per area, sometimes referred to as areal BMD. Bone mineral content and BMD are often measured for specific areas of the body, such as spine, hip, and femoral neck. Dual-energy X-ray absorptiometry (DXA) is considered the gold standard for measuring BMC and BMD in vivo and can be used on the whole body or at specific sites, such as the hip, spine, wrist, and femoral neck.

Bone mass varies by site within an individual and different sites have been found to have different associations with fracture risk. For example, in one study the trochanter (part of the femur) was more strongly associated with hip fracture (odds ratio [OR] 2.6, 95% confidence interval [CI] 2.0, 3.3) than the femoral neck (OR 1.9, 95% CI 1.5, 2.3) (9). Because of these differences, studies on the correlates of BMC and BMD may have different results based on measurement site used. Whole body measurements may be

most accurate, as measurements of specific sites depend on isolating parts of the body and may create more inter-individual measurement error (10).

In women, body weight is the strongest predictor of BMD. Other important factors include diet, physical activity, genetics, and family history (11). McGuigan et al. (2002) found that body weight accounted for 16.4% of the variance in spine BMD and 8.4% of the variance in femoral neck BMD among young women near their peak bone mass (11). Neville et al. (2002) found that among women, calcium intake was positively associated with femoral neck BMD among adolescents, and vitamin D intake was associated with both lumbar spine BMD during adolescence and femoral neck BMD during young adulthood (12). Cooper et al. (1995) found that physical activity was positively associated with femoral neck BMD (13). Oral contraceptive use in young women has been inversely associated with BMD (14).

A woman's own birth weight might also be associated with peak bone mass. This relationship could potentially be mediated by programming of the skeletal envelope by insulin-like growth factor I (IGF-I), an important factor during intrauterine life that is essential for bone metabolism (15-18). Epidemiologic studies have found inconsistent relationships between birth weight and BMC and BMD among women of all ages, including early adulthood when peak bone mass is achieved. Results have differed by site of bone measurement, whether BMC or BMD was evaluated, and covariates considered. Adult body size is associated with both birth weight and bone mass and it is unclear if there is an association between birth weight and bone mass independent of body size (Figure 1). Information on whether birth weight is independently associated with peak bone mass would improve the current understanding of the physiology of

attainment of peak bone mass. This cross-sectional study examined the association of birth weight with BMC and BMD in college-aged women using data from the University of Massachusetts (UMass) Vitamin D Status Study.

CHAPTER II

REVIEW OF THE LITERATURE

A. Physiology of the Association between Birth Weight and Bone Mass

The potential mechanism through which birth weight could be associated with later peak bone mass and density is poorly understood but is likely related to hormonal factors. Some evidence suggests that insulin-like growth factors (IGFs) contribute to the association between birth weight and bone mass. Insulin-like growth factors mediate growth hormone action throughout the body and the IGF system is the most important endocrine determinant of fetal growth (19). The availability of adequate glucose across the placenta is the most important determinant of fetal IGF-I concentrations, and so maternal nutrition can influence fetal growth through IGF-I concentrations (20).

Intrauterine programming of bone was assessed in one study in rats by giving dams control or low protein diets during pregnancy (21). At four weeks of age, female offspring in the restricted diet group showed a significantly lower level of serum IGF-I concentrations compared to controls; no differences were observed among the male offspring. At 75 weeks of age, the female offspring showed differences in bone structure and density at various sites. As compared to controls, female offspring in the restricted group had femoral heads with thinner, less dense trabeculae, femoral necks with closer packed trabeculae, vertebrae with thicker, denser trabeculae, and midshaft tibiae with denser cortical bone. In addition, the femoral heads and midshaft tibiae were structurally weaker and the femoral necks and vertebrae were structurally stronger, based on mechanical testing (22). The nutritional environment altered IGF-I concentrations and

skeletal development but it was not clear why the effect was only observed among females or why the differences in bone structure and density varied by site.

Javaid et al. (2004) found that umbilical venous IGF-I was positively associated with birth weight and bone size and, to a lesser extent, BMC in human newborns. They concluded that umbilical cord IGF-I concentration is a determinant or correlate of skeletal size rather than volumetric bone density. In a study of 100 infants born to healthy, nonsmoking women in Turkey, Akcakus et al. (2006) measured whole body BMC and BMD within 24 hours of birth, and measured cord serum IGF-I and maternal serum IGF-I obtained within 10 minutes of delivery. They found that birth weight was positively associated with cord serum IGF-I levels and whole body BMC and BMD. Whole body BMC and BMD were positively associated with cord serum IGF-I levels and maternal serum IGF-I levels in univariate but not multivariable analyses (23).

Studies in mice have shown that IGF-I is important in the acquisition of peak bone mineral density (BMD). Rosen et al. (1997) studied circulating and skeletal IGF-I levels and femoral BMD in two common inbred strains of mice with unexplained differences in femoral BMD. The authors found that serum and skeletal IGF-I levels and in vitro bone cell production of IGF-I were higher in mice from the strain with higher BMD, and suggested that the strain differences in BMD might be related to increased systemic and skeletal IGF-I in the strain with higher BMD. Rosen et al. (2004) showed reduced peak bone mass in a congenic strain of mice with reduced circulating IGF-I levels, further demonstrating that IGF-I is associated with a mechanism that contributes to BMD. As in the mice models, human BMD could potentially be associated with in

utero exposure to IGF-I; however, to date human studies have only considered the association among neonates.

It is also not clear how the association of adult body size and composition with birth weight and bone mass might be associated with exposure to IGF-I. Birth weight is positively associated with adult weight, height, and lean mass (24-27). The association between birth weight is less consistent; both weak negative (25) and positive (26) as well as null associations(25) have been reported. Among males and females born very preterm (<32 weeks gestation) birth weight was positively associated with weight, height, and fat free mass at 19 years but not with fat mass, percentage body fat, or fat distribution (24). Birth weight was also positively associated with adult height, weight, and fat free mass among males and females, and weakly associated with adult fat mass and percentage of body fat among females only, in a population from Guatemala (26).

Adult body composition is the strongest predictor of BMC and BMD (11, 28-30). Increased body weight is associated with increased BMD among women (11, 29). Height, lean mass, and fat mass are positively associated with BMC;(30) one study found lean mass to be a stronger predictor of BMC than height, weight, or fat mass (28). Given that adult size is associated with both birth weight and bone mass, associations between birth weight and bone mass could be mediated by adult size or another pathway might exist. In utero exposure to IGF-I might be a separate pathway by which birth weight could be associated with bone mass. Cord blood IGF-I levels at birth were not associated with IGF-I levels in children in one study (31) and other studies have found no association between birth weight and IGF-I levels in childhood (32) or adulthood (33, 34). Thus, an association between birth weight and adult bone mass could be a result of fetal

programming of skeletal metabolism and persisting effects of altered skeletal growth and development rather than a lasting change in IGF-I levels (15). Insulin-like growth factor I has been positively associated with current weight and height in children (31, 32) and adults (33) and inversely associated with adiposity in some studies (33, 34) but not others (31). However, as there seems to be a lack of connection between in utero and later IGF-I levels, this could represent an independent pathway through which birth weight is associated with bone mass.

B. Epidemiology of the Association between Birth Weight and Bone Mass

The association between birth weight and bone mass has been considered in a variety of populations with varying results. The existing studies are summarized in Table 1. The association has been considered among prepubescent children, young adults, and older adults.

A total of five studies have considered the association between birth weight and BMC and BMD among populations in which participants were likely at or near peak bone mass. Similar to studies in other populations, results varied by whether BMC or BMD was evaluated, the site of bone measurement, and what other factors were considered in statistical models. Among a population of 153 women aged 21 years from England, no statistically significant association between birth weight and BMC or BMD at the lumbar spine or femoral neck was observed (13). Among 282 36-year old men and women from Amsterdam, birth weight was significantly positively associated with BMC of the hip ($\beta=2.24$, $p\leq 0.05$) and the total body ($\beta=189.1$, $p\leq 0.05$), but neither association

was statistically significant after adult body weight was included in the regression model (35). No associations were observed between birth weight and BMD.

Large studies of women who are close to peak bone mass have higher power to detect modest associations between birth weight and BMC and BMD than studies of small size. Laitinen et al. (2004) conducted a longitudinal study among a subpopulation of the Northern Finland 1966 birth cohort, including 539 women (36). Birth weight was measured and recorded immediately after birth. Bone mineral content and BMD were measured at age 31 in the distal and ultradistal radius by DXA. Among women, birth weight was weakly but significantly positively correlated with distal BMC ($r=0.11$, $p=0.0095$). Data for the association between birth weight and BMD were not available, and the association with BMC was not corrected for adult body size.

Women younger than age 31 might be closer to peak bone mass and thus be a better study population. Saito et al. (2005) conducted a prospective cohort study among 86 female first-year students at Niigata Health and Welfare University, Japan (37). Weight at birth was obtained from the maternity record book and bone mass was measured by DXA at the lumbar spine and left hip, including the femoral neck. In correlation analyses, birth weight was significantly positively associated with BMC at all sites and with BMD at the femoral neck, but not lumbar spine or total hip. After adjustment for weight gains during various periods of childhood, current weight, calcium intake, metabolic equivalent (MET) index, and past exercise habits, birth weight was a significant predictor of BMC at the lumbar spine ($\beta=3.48$, $P = 0.0474$) and total hip ($\beta = 2.25$, $P =0.0352$) but not of femoral neck BMC, or of BMD at any site. The sample size was fairly small in this study and total body BMC and BMD were not available.

In the most recent study on birth weight and BMD, Leunissen et al. (2008) conducted a prospective cohort study comprising 191 females aged 18-24 years randomly selected from hospitals in the Netherlands. The authors obtained birth weight from hospital records, community health services, and general practitioners and used DXA to measure BMD of the total body (TB) and lumbar spine (LS). Birth weight, in SD-scores, was not a significant predictor of BMD_{TB} ($\beta = -0.38$, $P = 0.471$) but was a significant inverse predictor of BMD_{LS} ($\beta = -1.80$, $P = 0.026$).⁽³⁸⁾ The association remained significant when adjusted for weight ($\beta = -1.65$, $P = 0.037$) and when adjusted for lean body mass and fat mass rather than weight ($\beta = -2.11$, $P = 0.007$) but not when adjusted for change in weight and height ($\beta = 0.19$, $P = 0.866$). Unlike other studies, the association between birth weight and BMD_{LS} was inverse.

Two studies among prepubescent children found a significant association between birth weight and BMC and BMD. Among 330 eight-year-old children in Tasmania, birth weight was associated with BMC and BMD at the femoral neck but not lumbar spine (Jones & Dwyer 2000) ⁽³⁹⁾. Among 476 ten-year-old black and white South African children, an association was observed between birth weight and BMC and also bone area (which, together with BMC, determines BMD), although BMC and bone area were not significantly related among females in an adjusted model ⁽⁴⁰⁾.

Studies among adults have generated a variety of results. Four studies evaluated this relationship among women near or after menopause, when bone loss is the greatest among women. Among a population of 189 women aged 63-73 years in the United Kingdom (UK), no significant association between birth weight and BMC or BMD at the lumbar spine or femoral neck was observed, although results for BMC at the lumbar

spine approached statistical significance (p for trend 0.056) (41). Whole body BMC or BMD were not considered. Several other studies among older women found birth weight to be significantly associated with BMC but not BMD in unadjusted models, and the association was usually attenuated or eliminated after control for adult body weight. In a study of 305 postmenopausal women in the US, birth weight was positively correlated with age-adjusted BMC at the forearm ($r=0.15$, $p=0.002$), hip ($r=0.12$, $p=0.04$), and lumbar spine ($r=0.18$, $p=0.002$), but not the wrist ($r=0.04$, $p>0.10$); however, results were null after adjustment for age (42). Age-adjusted BMC measurements of the forearm, hip, and spine also increased with birth weight tertiles (p for trends <0.01 , <0.02 , and <0.01 , respectively); adjusting for adult weight attenuated the association for the forearm and hip but not spine. Age-adjusted BMD showed the same trend with birth weight tertiles as BMC at the forearm ($p<0.01$) and spine ($p<0.02$), but not hip or wrist ($p>.010$), and the association was eliminated after adjustment for adult weight. Again, whole body BMC and BMD were not considered. Among 468 women from the UK aged 60 to 70 years, birth weight was associated with BMC at the proximal femur ($r=0.16$, $p=0.0008$) and lumbar spine ($r=0.11$, $p=0.03$) but not with BMD at either site; data were not adjusted for adult body weight (43). Among 218 women aged 49-51 years in the UK, birth weight was positively associated with bone area ($p<0.001$) but not BMD, and the association was not significant after adjustment for adult body size (44). Overall, these studies did not consider total body BMC and BMD which might have resulted in increased measurement error and limits comparisons between studies of different sites.

In summary, epidemiologic studies have found inconsistent results regarding the association between birth weight and BMC and BMD, with birth weight often associated

with BMC but not BMD (13, 35-44). Among studies of young adults, results have ranged from no association, to a weak positive association between birth weight and BMC that was attenuated when adult weight was included in analyses, to a significant inverse association between birth weight and BMD. Peak bone mass has two components: the size of the skeletal envelope and the bone density within that envelope (13). Bone mineral content might better reflect the growth trajectory of the envelope that is influenced by early life factors, while bone mineral density might better reflect bone accrual in response to locally acting factors such as mechanical loading, possibly explaining why an association with birth weight is more frequently seen with BMC than with BMD. However, the trajectory of the skeletal envelope is also influenced by height and as bone area is associated with height, BMD is partially adjusted for height, which could also explain why birth weight is more strongly associated with BMC than with BMD (13, 35). Overall, study subjects have ranged in age from 8 to 89 and bone measurement sites have varied, and have often not included total body measurements which might be subject to less measurement error, making comparisons between studies difficult. The question of whether there is a pathway independent of adult body size or composition that explains part of the association between birth weight and bone mass has not been answered.

C. Summary

Osteoporosis causes a large disease burden in the US, both in terms of morbidity and health care costs for fractures, and disproportionately affects women. A better understanding of the factors that affect bone development could help improve strategies

to prevent or better treat osteoporosis. Birth weight may be associated with high peak bone mass, potentially reflecting programming by hormone exposure in utero. The physiology of the association between birth weight and bone mass is poorly understood but might be related to the action of IGF-I. Epidemiologic studies have been inconsistent, finding significant results more often for BMC than BMD and nonsignificant results when predictors such as body size at time of bone mass measurement were included in the analysis. However, it is still unclear whether adjustment for body size is appropriate. Adjustment for body size allows for the consideration of independent pathways linking birth weight to bone mass. Studies differ regarding location, age of subjects, and location of bone measurements, and generally only more recent studies have considered total body bone mass, which might reduce measurement error. This study included US women at or near peak bone mass and considered total body BMC and BMD.

CHAPTER III

METHODS

A. Specific Aim and Hypotheses

Aim: Using a cross-sectional design, we examined the association between birth weight and current bone mineral content (BMC) and bone mineral density (BMD) when adjusted and not adjusted for body composition among college-aged women.

Hypotheses:

1. Among college-aged women, birth weight will be positively associated with current total body BMC both when and when not adjusted for body composition.
2. Among college-aged women, birth weight will be positively associated with current total body BMD both when and when not adjusted for body composition.

B. Study Design, Setting, and Population

Using a cross-sectional design, we assessed the association between birth weight and bone density among Amherst-area women aged 18 to 30. Data were from the University of Massachusetts Vitamin D Status Study, a cross-sectional study conducted from March 2006 to May 2008 to assess vitamin D status in young women and to identify its dietary, environmental, and lifestyle determinants. During the late luteal phase of their menstrual cycle, participants attended a single study visit during which they completed two self-report questionnaires, received a DXA scan, and had anthropomorphic measurements taken at Arnold House and University Health Services on the University of Massachusetts Amherst campus. Participants then emailed the investigators the start date of their next menstrual period.

The Amherst area includes five colleges: University of Massachusetts Amherst, Amherst College, Hampshire College, Mount Holyoke College, and Smith College. As of the 2000 census, the population of Amherst, where most of the colleges are based, was 34,874, of which 6,117 was females aged 20-29.(45) The college population was 26,403.(46) Of the total Amherst population, 79.3 percent was white, 5.1 percent was black, and 9.1 percent was Asian or Pacific Islander.(45)

C. Subject Ascertainment

Participants were recruited from the UMass campus and Amherst area by flyers posted throughout the five colleges. Inclusion criteria for entry into the study were being female, aged 18-30 years, having menstrual periods, not being pregnant, and not currently experiencing untreated depression. Exclusions were: 1) diagnosis of high blood pressure, kidney disease, liver disease, bone diseases such as osteopenia or osteomalacia, digestive disorders such as celiac disease, Crohn's disease, or uncreative colitis, rheumatologic diseases such as rheumatoid arthritis, multiple sclerosis, thyroid disease such as Grave's disease, hyperthyroidism, hypothyroidism, or benign thyroid nodules, cancer, type 1 or type 2 diabetes, hyperparathyroidism, elevated cholesterol or hyperlipidemia, polycystic ovaries or polycystic ovarian syndrome and 2) self-reported use of medications including prednisone, anabolic steroids, and anticonvulsants such as depakote, Tagamet or Cimetidine, or Propranolol. These criteria were designed to restrict the study population to college-aged women without health conditions or medications that could affect vitamin D levels. For the purpose of the proposed analysis, we also excluded participants with missing data on birth weight and DXA scan results.

D. Birth Weight Assessment

The primary exposure in this study was the birth weight of the participant. Birth weight was assessed by self-report on the questionnaire completed during the study visit. The question asked for birth weight in the following categories: less than 5.5 pounds, 5.5 to 6.9 pounds, 7.0 to 8.4 pounds, 8.5 to 9.9 pounds, 10 pounds or more, or not sure (Table 1). Women who were not sure of their birth weight were invited to consult with family members by phone call while completing questionnaires, or obtain this information after the study visit and report birth weight by email. The birth weight question was added to one study questionnaire after the first six months of recruitment. Thus, the first 30 participants did not have this information available.

The validity of self-reported birth weight has been investigated previously. Troy et al. (1996) found that self-reported birth weight was correlated with birth weight reported on state birth records (Spearman $r=0.74$) and birth weight report by the subject's mother was also correlated with state records (Spearman $r=0.85$).⁽⁴⁷⁾ Thus we believe that self-reported birth weight is an accurate measure of participants' actual birth weight.

E. Bone Mass Assessment

The outcomes of this study were BMC and BMD, both of which were assessed by DXA scan. The DXA instrument was calibrated daily with a phantom and all scans were performed by the same study research assistant. Total body BMC were measured in grams and total body BMD was measured in g/cm^2 .

Dual-energy X-ray absorptiometry is considered the gold standard for measuring bone density. Among female rats, the femur densities calculated by the former standard, an application of Archimides' principle, was highly correlated for both DXA BMD ($r=0.82$, $p < 0.0001$) and DXA BMC ($r=0.87$, $p < 0.0001$).⁽⁴⁸⁾ Short-term variability of BMD in humans is low; in a study of healthy subjects aged 22-63, the coefficient of reliability was 0.99 for the lumbar spine and 0.97 for the femoral neck (49).

F. Covariate Assessment

Body size, diet, and physical activity are predictors of bone density and were assessed during the clinic visit (11). Height was measured using a stadiometer while the participant was not wearing shoes. Weight was measured using a calibrated scale while the participant was wearing minimal indoor clothing and no shoes. Waist circumference was measured using a standard tape measure. Calcium and vitamin D intake in the past two months from both diet and supplements were assessed with a modified version of the Harvard food frequency questionnaire. Current physical activity was determined using questions developed for the Nurses' Health Study and scored using metabolic equivalent units (METs), as defined by Ainsworth et al. (1993) (50). In addition, age, race, smoking status, alcohol use, age at menarche, and oral contraceptive use were evaluated. Height, weight, calcium and vitamin D intake, physical activity, age at menarche, and age were evaluated continuously. Race was measured categorically as white or non-white, smoking status and alcohol use as ever/never, and OC use as past/current/never.

G. Statistical Analysis

1. Bone Mineral Content

a. Specific Aim 1:

To examine the association between birth weight and current BMC among college-aged women.

b. Hypothesis 1:

Birth weight will be positively associated with current total body BMC both when and when not adjusted for body composition among college-aged women.

c. Univariate Analysis

We presented the number and percent of subjects excluded for missing exposure and outcome data (Table 2) and the characteristics of those with and without exposure and outcome data (Table 3).

We calculated the number and percent of those in each category of birth weight (Table 4) and the mean and standard deviation of BMC, as well as the number and percent above and below the mean BMC (Table 6).

d. Bivariate Analysis

We determined the mean and standard deviation of continuous covariates and the frequency and percent of categorical covariates within categories of exposure (Table 5) and outcome (Table 7) variables. We used analysis of variance (ANOVA) to evaluate differences in continuous covariates between categories. Chi square tests were used to

assess differences in the distribution of covariates assessed categorically, with Fisher's Exact test used when cell counts were less than five.

Linear regression was used to estimate unadjusted beta coefficients and standard errors to evaluate the crude association between birth weight and BMC (Table 8), as well as between other covariates and BMC (Table 9), using t-tests to determine if the covariate was predictive of BMC. Logistic regression was used to determine unadjusted odds ratios and 95% confidence intervals to provide a crude association between birth weight and BMC dichotomized at the sample mean (Table 11), as well as other covariates and BMC dichotomized at the sample mean (Table 12), using likelihood ratio tests to determine if the covariate was predictive of BMC.

e. Multivariable Analysis

Multivariable linear regression was used to model the relation between birth weight and BMC evaluated continuously, while adjusting for confounding effects of other factors 1) without body composition and 2) with body composition (Table 10). Variables retained in the model were chosen using backwards selection. Covariates with a t-test $p < 0.25$ in the bivariate models were included in the initial multivariable model and covariates with an adjusted t-test $p < 0.05$ were retained in the final model. Birth weight was retained in the model regardless of significance. We estimated beta coefficients, standard errors, and p-values.

Multivariable logistic regression was used to model the relation between birth weight and BMC evaluated as a dichotomous variable, while adjusting for confounding effects of other factors, both without and with factors related to body composition

included (Table 13). Variables retained in the model were chosen using backwards selection. Covariates with a likelihood ratio test $p < 0.25$ in the bivariate models were included in the initial multivariable model and covariates with an adjusted likelihood ratio test $p < 0.05$ were retained in the final model. Birth weight was retained in the model regardless of significance. We estimated odds ratios and 95% confidence intervals. We used fractional polynomials to determine if continuous covariates retained in the model were linear in the logit. We used the Hosmer-Lemeshow Goodness-of-Fit test to determine if there was significant lack of fit at $p = 0.05$. We used the receiver operating characteristic (ROC) curve to determine the discrimination of the logistic models. We plotted the delta deviance by the predicted probabilities to reveal any poorly fit points and Pregibon's delta Beta to reveal any influential observations.

2. Bone Mineral Density

a. Specific Aim 2:

To examine the association between birth weight and current bone mineral density (BMD) among college-aged women.

b. Hypothesis 2:

Birth weight will be positively associated with current total body BMD both when and when not adjusted for body composition among college-aged women.

c. Univariate Analysis

We followed the same analytic methods as for specific aim 1. We calculated the mean and standard deviation of BMD, as well as the number and percent above and below the mean BMD (Table 14).

d. Bivariate Analysis

We determined the mean and standard deviation of continuous covariates and the frequency and percent of categorical covariates within categories of exposure (Table 5) and outcome (Table 15) variables. We used ANOVA to evaluate differences in continuous covariates between categories. Chi square tests were used to assess differences in the distribution of covariates assessed categorically, with Fisher's Exact test used when cell counts were less than five.

Linear regression was used to estimate unadjusted beta coefficients and standard errors to provide a crude association between birth weight and BMD (Table 16), as well as between other covariates and BMD (Table 17), using t-tests to determine if the covariate was predictive of BMD. Logistic regression was used to determine unadjusted odds ratios and 95% confidence intervals for the crude association between birth weight and BMD dichotomized at the sample mean (Table 19), as well as between other covariates and BMD dichotomized at the sample mean (Table 20), using likelihood ratio tests to determine if the covariate was predictive of BMD.

e. Multivariable Analysis

Multivariable linear regression was used to model the relation between birth weight and BMD evaluated continuously, while adjusting for the confounding effects of other factors, both without and with factors related to body composition included (Table 18). Variables retained in the model were chosen using backwards selection. Covariates with a t-test $p < 0.25$ in the bivariate models were included in the initial multivariable model and covariates with an adjusted t-test $p < 0.05$ were retained in the final model. Birth weight was retained in the model regardless of significance. We estimated beta coefficients, standard errors, and p-values.

Multivariable logistic regression was used to model the relation between birth weight and BMD evaluated as a dichotomous variable, while adjusting for the confounding effects of other factors 1) without body composition and 2) with body composition (Table 21). Variables retained in the model were chosen using backwards selection. Covariates with a likelihood ratio test $p < 0.25$ in the bivariate models were included in the initial multivariable model and covariates with an adjusted likelihood ratio test $p < 0.05$ were retained in the final model. Birth weight was retained in the model regardless of significance. We estimated odds ratios and 95% confidence intervals. We used fractional polynomials to determine if continuous covariates retained in the model were linear in the logit. We used the Hosmer-Lemeshow Goodness-of-Fit test to determine if there was significant lack of fit at $p = 0.05$. We used the ROC curve to determine the discrimination of the logistic models. We plotted the delta deviance by the predicted probabilities to reveal any poorly fit points and Pregibon's delta Beta to reveal any influential observations.

3. Effect Modification

We considered effect modification by body composition. We first conducted stratified analyses to evaluate whether the associations differed among women below and above the mean waist circumference. We then created a multiplicative interaction term by multiplying the categorical birth weight term by the dichotomous waist circumference term. We evaluated the significance of the interaction term in linear models using the Wald test and in logistic models using the likelihood ratio test.

4. Subanalyses

We conducted subanalyses excluding women in the highest and lowest birth weight categories (n=5) as birth weight could have a different association with BMC and/or BMD at more extreme values of birth weight. We also conducted subanalyses among white women only.

Statistical analyses were performed using Stata version 10.0 (Stata Corporation, College Station, TX) software.

H. Human Subjects Protection

Participants signed an informed consent form indicating that they understood that participating in the study entailed having blood drawn and having a DXA scan, that if they chose to participate they could refuse to answer any questions and withdraw at any time, and that researchers had answered any questions they had. To safeguard confidentiality, all of the information provided by participants was coded by ID number

only. Identifying information was stored in locked filing cabinets and kept separate from study data to prevent an inadvertent breach in confidentiality.

The risks of participating in this study were those associated with having blood pressure taken, blood drawn, urine collected, and undergoing a DXA scan. For having blood pressure taken, the procedure may have caused some mild discomfort as the blood pressure cuff was inflated. For having blood drawn, risks included pain at the site of needle entry, occasional bruising at the site, and rarely, fainting. Risk of infection was minimal since only sterile one-time-use equipment was used. There were minimal risks associated with providing a urine sample. The collection of a drop of blood with a lancet may have caused minimal pain and bleeding. For the DXA scan, the risk from exposure to low-dose radiation is very small and is about the same as would occur in a flight between Boston and Los Angeles.

Subjects were provided with information concerning their hemoglobin and blood sugar levels, a written copy of the results of the analyzed diet questionnaire, the opportunity to receive dietary counseling from a senior or graduate nutrition student, and a copy of the DXA results, which indicated body composition and bone mineral density, which may provide some information on risk of osteoporosis later in life. Upon completion of all testing sessions, participants received \$10.00. The Institutional Review Board at the University of Massachusetts Amherst has approved the protocol for this study.

I. Permission to Access Data

Permission to access the Vitamin D Status Study data was granted by principal investigators Alayne Ronnenberg, ScD, Department of Nutrition, and Elizabeth Bertone-Johnson, ScD, Department of Public Health, University of Massachusetts Amherst.

CHAPTER IV

RESULTS

Of the 186 women in the Vitamin D Status Study, 149 were included in the current analysis. Seven were excluded for reporting “don’t know” to birth weight and 30 were excluded for not reporting birth weight; no additional exclusions were made (Table 2). As compared to women included in the current analysis, those excluded were similar in terms of age ($p=0.19$), height ($p=0.97$), weight ($p=0.30$), and race ($p=0.72$) (Table 3).

Birth weight was collapsed into three categories due to small numbers in the lowest ($n=2$) and highest ($n=3$) categories. There were 38 (25.5%) women with a birth weight of less than 7 pounds, 78 (52.4%) women between 7 and 8.4 pounds, and 33 (22.1%) women greater than 8.4 pounds (Table 4). With increasing birth weight category, mean weight and mean waist circumference increased ($p=0.02$ and $p=0.01$, respectively); other covariates were similar across categories (Table 5).

The mean (standard deviation [SD]) of BMC was 2,567.6 (378.1) g, with 74 women below the mean and 75 above (Table 6). Based on visual inspection of the histogram and the normal probability plot, BMC was distributed normally. Height, weight, BMI, waist circumference, and dark meat fish consumption were significantly associated with BMC. Other covariates were not significantly associated with BMC (Table 7); for example, women below the mean BMC had a mean (SD) weight of 58.0 (7.8) kg and women above the mean BMC had a mean (SD) weight of 70.6 (8.4) kg ($p<0.01$).

Univariate linear regression revealed a positive association between birth weight and BMC. The beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds

was 110.5 (73.2) g ($p=0.13$) and for women with a birth weight of 8.5 pounds or greater was 257.7 (88.0) g ($p<0.01$) (Table 8). Increased BMC was observed among women with greater height ($p>0.01$), greater weight ($p>0.01$), greater waist circumference ($p>0.01$), greater dark meat fish consumption ($p=0.01$), and greater physical activity ($p=0.03$) (Table 9).

When not including body size factors, predictors in the final model were birth weight and dark meat fish consumption (model 1) (Table 10). Birth weight was significantly associated with BMC in the final model without body size factors; the beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds was 119.7 (71.4) g ($p=0.10$) and for women with a birth weight of 8.5 pounds or greater was 279.6 (86.1) g ($p<0.01$). The beta coefficient (SE) for dark meat fish consumption was 774.3 (263.6) g/servings/day ($p<0.01$).

When including body size factors, predictors in the final model were birth weight, height, weight, waist circumference, age at menarche, and dark meat fish consumption (model 2) (Table 10). Birth weight was not significantly associated with BMC in the final model with body size factors: the beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds was 48.9 (43.1) g ($p=0.26$) and for women with a birth weight of 8.5 pounds or greater was 84.8 (53.5) g ($p=0.12$). Dark meat fish consumption was the strongest predictor of BMC with a beta coefficient (SE) of 395.9 (162.2) g/servings/day ($p=0.02$). Height and weight were positively associated with BMC, with beta coefficients (SEs) of 22.2 (3.7) g/cm ($p<0.01$) and 26.7 (4.0) g.kg ($p<0.01$), respectively. Waist circumference and age at menarche were inversely associated with BMC, with beta coefficients (SEs) of -12.1 (4.1) g/cm ($p<0.01$) and -37.5 (13.6) g/year ($p<0.01$).

Univariate logistic regression suggested no significant association between birth weight and BMC dichotomized at the mean (Table 11). As compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had a 10% lower odds of having higher BMC (odds ratio [OR] 0.9, 95% confidence interval [CI] 0.4-2.0) and women with a birth weight of 8.5 pounds or greater were more than twice as likely to have higher BMC (OR 2.2, 95% CI 0.9-5.8). Higher BMC was positively associated with height, weight, BMI, waist circumference, and dark meat fish consumption (Table 12).

Birth weight was positively associated with BMC in the final model not including body size factors (model 3): as compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had similar odds of having higher BMC (OR 1.0, 95% CI 0.5-2.4) and women with a birth weight of 8.5 pounds or greater were more than twice as likely to have higher BMC (OR 2.8, 95% CI 1.0-7.7) (Table 13). When not including body size factors, predictors in the final model were birth weight, race, and dark meat fish consumption.

Birth weight was not associated with BMC in the final model including body size factors (model 4): as compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had reduced odds of having higher BMC (OR 0.7, 95% CI 0.2-2.4) and women with a birth weight of 8.5 pounds or greater were had increased odds of having higher BMC (OR 1.9, 95% CI 0.4-8.3) (Table 13). When including body size factors, predictors in the final model were birth weight, weight, waist circumference, and age at menarche.

Based on fractional polynomials, dark meat fish consumption was found to be linear in the logit and so was kept as continuous in the model not including body size factors (model 3). The results of the Hosmer-Lemeshow Goodness of Fit test showed that there was no evidence of significant lack of fit ($p=0.50$). The ROC curve revealed adequate discrimination with an area under the curve of 0.67. Plotting the delta deviance by predicted probabilities revealed no poorly fit points. Pregibon's delta Beta revealed 55 influential observations; however, results were similar when these observations were excluded.

Based on fractional polynomials, weight, waist circumference, and age at menarche were found to be linear in the logit and so were kept as continuous in the model including body size factors (model 4). The results of the Hosmer-Lemeshow Goodness of Fit test show that there is evidence of significant lack of fit ($p=0.001$). The ROC curve revealed excellent discrimination with an area under the curve of 0.98. Plotting the delta deviance by predicted probabilities revealed 3 poorly fit points; however, results were similar when these observations were excluded. Pregibon's delta Beta revealed 3 influential observations; however, results were similar when these observations were excluded.

The mean (SD) of BMD was 1.16 (0.08) g/cm^2 , with 71 women below the mean and 78 above (Table 14). Based on visual inspection of the histogram and the normal probability plot, BMD was distributed normally. Values of BMD were similar to the mean (SD) of the reference population used by the DXA scan of 1.13 (0.08) g/cm^2 . Height, weight, BMI, waist circumference, and dark meat fish consumption were significantly associated with BMD; other covariates were not significantly associated

with BMD (Table 15). For example, women below the mean BMD had a mean (SD) weight of 60.0 (9.3) kg and women above the mean BMD had a mean (SD) weight of 68.3 (9.4) kg ($p<0.01$).

Univariate linear regression revealed a slight positive association between birth weight and BMD: the beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds was 0.02 (0.02) g ($p=0.23$) and for women with a birth weight of 8.5 pounds or greater was 0.05 (0.02) g ($p=0.01$) (Table 16). Increased BMD was observed among women with greater height ($p<0.01$), weight ($p<0.01$), waist circumference ($p<0.01$), dark meat fish consumption ($p=0.02$), and physical activity ($p<0.01$), and decreased BMD was observed among women with later age at menarche ($p=0.01$) (Table 17).

When not including body size factors, predictors in the final model were birth weight, dark meat fish consumption, physical activity, and age at menarche (model 5) (Table 18). Birth weight was statistically significant in the final model without body size factors: the regression coefficient (SE) for women with a birth weight of 7 to 8.4 pounds was 0.02 (0.02) g/cm^2 ($p=0.17$) and for women with a birth weight of 8.5 pounds or greater was 0.05 (0.02) g/cm^2 ($p<0.01$). The beta coefficients (SEs) for dark meat fish consumption, physical activity, and age at menarche were 0.15 (0.06) $\text{g/cm}^2/\text{serving}/\text{day}$ ($p=0.01$), 0.0004 (0.0001) $\text{g/cm}^2/\text{MET-hours}/\text{week}$ ($p<0.01$), and -0.01 (0.01) $\text{g/cm}^2/\text{year}$ ($p<0.01$), respectively.

When including body size factors, predictors in the final model were birth weight, weight, waist circumference, physical activity, and age at menarche (model 6) (Table 18). Birth weight was not statistically significant in the final model including body size factors: the regression coefficient (SE) for women with a birth weight of 7 to 8.4 pounds

was 0.01 (0.01) g/cm² (p=0.37) and for women with a birth weight of 8.5 pounds or greater was 0.03 (0.02) g/cm² (p=0.11). Weight and physical activity were positively associated with BMD with beta coefficients (SEs) of 0.007 (0.001) g/cm²/kg and 0.0003 (0.0001) g/cm² /MET-hours/week, respectively. Waist circumference and age at menarche were inversely associated with BMD with beta coefficients (SEs) of -0.004 (0.001) g/cm²/cm and -0.01 (0.004) g/cm²/year, respectively.

Univariate logistic regression revealed a significant association between birth weight and BMD dichotomized at the mean: as compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had a 20% higher odds of having higher BMD (OR 1.2, 95% CI 0.5-2.6), and women with a birth weight of 8.5 pounds or greater were more than twice as likely to have higher BMD (OR 2.8, 95% CI 1.1-7.6) (Table 19). Having higher BMD was positively associated with height, weight, BMI, waist circumference, and dark meat fish consumption (Table 20).

Birth weight was significantly positively associated with BMD in the final model not including body size factors (model 7). As compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had a 30% increased odds of having higher BMD (OR 1.3, 95% CI 0.6-2.9) and women with a birth weight of 8.5 pounds or greater were more than three times as likely to have higher BMD (OR 3.4, 95% CI 1.2-9.5). When not including body size factors, predictors in the final model were birth weight, age at menarche, and dark meat fish consumption.

Birth weight was not significantly associated with BMD in the final model including body size factors (model 8). As compared to women with a birth weight of less than 7 pounds, women with a birth weight of 7 to 8.4 pounds had a 10% increased odds

of having higher BMD (OR 1.1, 95% CI 0.5-2.8) and women with a birth weight of 8.5 pounds or greater were nearly three times as likely to have higher BMD (OR 2.7, 95% CI 0.9-8.4). When including body size factors, predictors in the final model were birth weight, weight, waist circumference, and age at menarche (Table 21).

In the model not including body size factors, use of fractional polynomials showed that age at menarche and dark meat fish consumption were linear in the logit and could be kept as continuous variables (model 7). The results of the Hosmer-Lemeshow Goodness of Fit test showed that there was no evidence of significant lack of fit ($p=0.51$). The ROC curve revealed adequate discrimination with an area under the curve of 0.69. Plotting the delta deviance by predicted probabilities revealed 10 poorly fit points; however, results were similar when these observations were excluded. Pregibon's delta Beta revealed seven influential observations; however, results were similar when these observations were excluded.

In the model including body size factors, use of fractional polynomials showed that weight, waist circumference, and age at menarche were linear in the logit and could be kept as continuous variables (model 8). The results of the Hosmer-Lemeshow Goodness of Fit test showed that there was no evidence of significant lack of fit ($p=0.10$). The ROC curve revealed adequate discrimination with an area under the curve of 0.80. Plotting the delta deviance by predicted probabilities revealed three poorly fit points; however, results were similar when these observations were excluded. Pregibon's delta Beta revealed no influential observations.

Stratified analyses to evaluate whether the associations differed among women below and above the mean waist circumference revealed no meaningful effect

modification (Table 22). For example, in the linear regression of BMC not including body size factors (model 1) the beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds was 57.1 (78.2) g ($p=0.11$) in those below the mean waist circumference and 186.8 (115.9) g ($p=0.11$) in those above the mean waist circumference, and for women with a birth weight of 8.5 pounds or greater was 213.4 (110.6) g ($p=0.06$) in those below the mean waist circumference and 207.7 (123.9) g ($p=0.10$) in those above the mean waist circumference.

Results were similar in the subanalysis excluding women in the highest and lowest birth weight categories ($n=5$). For example, in the linear regression of BMC not including body size factors (model 1) the beta coefficient (SE) for women with a birth weight of 7 to 8.4 pounds changed from 119.7 (71.4) g ($p=0.10$) to 100.0 (72.1) g ($p=0.12$) in the sensitivity analysis, and for women with a birth weight of 8.5 pounds or greater changed from 279.6 (86.1) g ($p=0.001$) to 235.7 (88.7) g ($p=0.009$) in the subanalysis.

Beta coefficients and odds ratios were similar in the subanalysis limited to white women. For example, in the linear regression of BMC not including body size factors (model 1) the regression coefficient (SE) for women with a birth weight of 7 to 8.4 pounds changed from 119.7 (71.4) g ($p=0.10$) to 114.6 (72.1) g ($p=0.11$) in the subanalysis, and for women with a birth weight of 8.5 pounds or greater changed from 279.6 (86.1) g ($p=0.001$) to 258.7 (86.1) g ($p=0.003$) in the subanalysis.

CHAPTER V

DISCUSSION

A. Consistency with Prior Literature

In this cross-sectional study of college-aged women, we found that birth weight was positively associated with BMC and BMD in analyses not adjusted for body size and composition. After adjustment for anthropometric factors, results were attenuated and birth weight was no longer significantly associated with BMC or BMD. This indicates that body size is the primary pathway through which birth weight is associated with BMC/BMD. After adjustment for body composition factors, birth weight was modestly associated with BMC and BMD. This may be due to residual confounding by body composition, or may indicate that birth weight may be related to peak bone mass through a mechanism other than through its effect on body composition. Additional studies with larger sample size and continuous evaluation of birth weight will be necessary to further investigate these relationships.

Our results are consistent with the majority of similar studies among young women. Three previous studies also found a significant positive association between birth weight and BMC; of these, one did not adjust for adult body size(36), the second found that the association was eliminated after adult weight was included in the model(35), and the third found that birth weight remained significantly associated with BMC after adjustment for current weight and other covariates at the lumbar spine and total hip but not femoral neck (37). Two studies did not find an association between birth weight and BMD (13, 35) and one study found a significant positive association between birth weight

and BMD at the femoral neck but not lumbar spine or total hip; adjustment for current weight and other covariates eliminated the association (37).

As found in previous studies, birth weight was more strongly associated with BMC than with BMD. Early life factors might influence the development of the skeletal envelope rather than the processes that contribute to bone accrual during later life, particularly adolescence. Additionally, bone mineral content is not corrected for body size; as body size is the primary if not sole reason for the association between birth weight and bone mass, the association would be expected to appear stronger for BMC as it is not size-adjusted, while BMD is BMC divided by bone area, which is associated with body size (13, 35). Future studies should evaluate bone mineral apparent density and height-adjusted bone mineral density, both of which are measures of bone that more closely approximate volumetric density. Evaluating these measures of bone mass might improve understanding of the true association between birth weight and bone density and whether a pathway exists independent of body size between birth weight and bone mass.

Weight and waist circumference were included together in adjusted models, which might be a proxy for fat free mass. Future studies should also consider fat free mass as compared to body weight to determine whether body size or body composition is more important in mediating the association of birth weight with bone mass, which would improve understanding of how peak bone mass is achieved.

B. Limitations

1. Nondifferential Misclassification

Nondifferential misclassification of birth weight may occur due to women incorrectly reporting their birth weight, for example if they had never been told, did not talk to a parent during or after the study visit, or had been told many years previously. As women would not be expected to know their BMC or BMD because DXA scans are not routinely performed on young women, such misreporting of birth weight would be expected to be nondifferential. The effect of such misclassification would be to underestimate any true association between birth weight and BMC and BMD. To aid women in remembering their birth weight we gave them the opportunity to contact another person, such as their mother, for this information. Recall of birth weight by the individual and by the individual's mother have been found to be correlated with true birth weight (47). In addition, exact birth weight was not queried and instead birth weight categories were provided. It may be easier for women to recall their birth weight within a range and therefore any misclassification would likely occur in adjacent categories of the true birth weight.

Nondifferential misclassification of BMC and BMD may occur due to measurement error in the DXA scan. This error is expected to be random and thus nondifferential. The effect of such misclassification would be to underestimate any true association between birth weight and BMC and BMD. However, the DXA scan is the gold standard for measuring BMC and BMD, the instrument was calibrated with a

phantom to minimize measurement error, and the same research assistant performed all scans. Therefore this possibility is unlikely.

2. Selection Bias

Selection bias could have occurred if women with relatively low birth weight as well as a history of broken bones (due to low BMC/BMD) were more concerned about their health and therefore more likely to participate than women with normal birth weight and normal BMC/BMD. This scenario, if it occurred, would inflate the observed association between birth weight and BMC and BMD. This scenario is unlikely, however, because most women were in the normal range of birth weights and the study excluded women with diagnosed osteomalacia (bone pain). In addition, BMC and BMD measures that are relatively low, but normal, are not associated with increased fractures among young women and young women rarely receive bone scans.

3. Information Bias

Information bias could have occurred if women with low BMC and/or BMD were more concerned about their health than women without these disorders, knew that low birth weight has been associated with poor health outcomes, and therefore reported their birth weight as lower than it truly was. This would overestimate the true association between birth weight and BMC and BMD. However, this is unlikely to occur because DXA scans are not commonly administered to young women, and therefore women were unlikely to know their BMC and BMD before completing the study. In addition, as part of the study protocol, the DXA was performed after the questionnaire for most

participants. Finally, the women were generally healthy and so not likely to be searching for reasons to explain their health.

4. Confounding

All subjects were females aged 18-30 present in the Amherst, MA, area from March 2006-May 2008. Potential confounders measured during the study visit were height, weight, dietary intake of calcium and vitamin D, physical activity, age, smoking status, alcohol use, and OC use. For example, height might be positively associated with birth weight and with BMC and BMD, resulting in positive confounding such that the crude association between birth weight and BMC and BMD overestimates the true association. We controlled for these in multivariable analyses; however, each of these factors is subject to measurement error; therefore, residual confounding is a concern. Although these factors encompass the main determinants of BMC and BMD, it is possible that we are missing information on another variable, such as family history, that may be a confounding factor or have inadequately controlled for one of the factors.

5. Temporality

In many cross-sectional studies it is unclear whether the exposure preceded the outcome or vice versa. Although this is a cross-sectional study, birth weight occurred before the attainment of BMC and BMD in young adulthood and so temporality is not a concern.

6. Survivor Bias

In studies where the outcome has occurred before participants are recruited, it is possible that potential subjects who experienced the outcome do not participate due to effects of the outcome (e.g., if the outcome caused morbidity that prevented people from participating or caused mortality). If having lower birth weight made women unable to participate, the association between birth weight and BMC and BMD would be underestimated. However, young women are unlikely to be affected by low BMC/BMD within normal ranges as it is not associated with morbidity or mortality at this age and these women are expected to be able to participate in the study as well as women with relatively higher BMC/BMD.

7. Statistical Limitations

As the Vitamin D Status Study is relatively small (n=186), a weakness of this analysis is that it is powered to detect an odds ratio of approximately 4.5. Power calculations were based on the dichotomous outcome, and we expect to have slightly greater power when we analyze BMC/BMD as continuous outcomes.

In addition, birth weight was measured as categorical which limits our ability to consider gradations of birth weight. We cannot analyze the association with very low birth weight as all birth weights <5.5 pounds are one category and we had very few women in this category.

8. Generalizability

The women who participated in the UMass Vitamin D Status Study consisted of young, predominantly white women who were healthy and more educated than the general population. However, it is unlikely that these factors influence the physiologic association between birth weight and BMC and BMD. We would therefore generalize to all women of similar age.

C. Significance

Birth weight was positively associated with BMC and BMD, though results were nonsignificant when adjusted for body size. This suggests that body size is the main and possible only factor that mediates the association between birth weight and bone mass. The results of this analysis contribute further knowledge of the association between birth weight and BMC and BMD. Future studies would benefit from increased sample size and access to birth records for birth weight and information on other early life factors. They should also further evaluate volumetric measures of bone density and body composition to determine if there is an association between birth weight and bone mass independent of body size and to better understand the development of bone mass.

Table 1. Summary of Existing Literature.

Author	Population	Study Design	Results: BMC	Results: BMD	Comments
Cooper et al. (1995)	N=153 women Mean age=21 years Mean birth weight=3.307kg	Prospective Cohort	Lumbar spine $r=0.12$, NS ¹ Femoral neck $r=0.14$ NS	Lumbar spine $r=0.05$ NS Femoral neck $r=0.05$ NS	
Cooper et al. (1997)	N=189 women Mean age=65.6 years Mean birth weight=3.460kg	Prospective Cohort	Age-adjusted: Lumbar spine p for trend=0.056 Femoral neck p for trend=0.21	Age-adjusted: Lumbar spine p for trend=0.14 Femoral neck p for trend=0.43	BMC and BMD analyzed in tertiles
Jones & Dwyer (2000)	N=115 girls, 215 boys Mean age=8 years Mean birth weight=2.764kg (girls)	Prospective Cohort	Data not shown, reported as similar to BMD	Femoral neck: $r=0.26$, $p<0.0001$ Lumbar Spine: $r=0.09$, $p=0.22$	Data combined for girls and boys
Yarbrough et al. (2000)	N=305 women Mean age=70.3 years Mean birth weight=3.4kg	Cross-sectional	Age-adjusted: Hip p for trend<0.02 Lumbar spine p for trend<0.01	Age-adjusted: Hip p for trend >0.10 Lumbar spine p for trend <0.02	
te Velde et al. (2004)	N=286 men and women Mean age=36.5 years Mean birth weight=3.42kg (women)	Prospective Cohort	Adjusted for gender: Hip $\beta=2.24$ $p\leq 0.05$ Total body $\beta=189.1$ $p\leq 0.05$	Adjusted for gender: Hip: $\beta=0.016$ NS Total body $\beta=0.018$ NS	Results NS when adjusted for body weight
Dennison et al. (2005)	N=468 women Mean age=66.4 years	Prospective Cohort	Proximal femur $r=0.16$, $p=0.0008$ Lumbar spine $r=0.11$, $p=0.03$	Proximal femur $r=0.02$, $p=0.62$ Lumbar spine $r=0.03$, $p=0.59$	Association between birth weight and BMC remained significant at the proximal femur after adjusting for covariates
Laitinen et al. (2005)	N=539 women Mean age=31 years	Prospective Cohort	Standardized distal radius and standardized birth weight: $r=0.11$, $P=0.0095$	Data not shown	Distal radius may not be comparable to hip and/or spine measurements

Continued on the next page

Pearce et al. (2005)	N=218 women Age=49-51 years Mean birth weight=3.38kg	Prospective Cohort	Not applicable	Hip: $\beta=0.01$ (95% CI -0.01, 0.03) ² Lumbar spine: $\beta=0.01$ (95% CI -0.01, 0.03)	
Saito et al., (2005)	N=86 women Mean age=18.9 years Mean birth weight=3.17kg	Prospective Cohort	Lumbar spine $r=0.30$ $p<0.01$ Femoral neck $r=0.25$ $p<0.05$ Total hip $r=0.32$ $p<0.01$;	Lumbar spine $r=0.21$ $p>0.05$ Femoral neck $r=0.23$ $p<0.05$ Total hip $r=0.15$ $p>0.05$	Study population from Japan and had lower height and weight as compared to studies among Western populations
Vidiluch et al. (2007)	N=222 girls Mean age=10.62 years (white), 10.53 years (black) Mean birth weight: 3.12kg (white), 3.03kg (black)	Prospective Cohort	Adjusted for age: Femoral neck p for trend NS Lumbar spine p for trend NS Whole body p for trend NS	Not applicable	Data analyzed separately by race, results were the same
Leunissen et al. (2008)	N=191 women Mean age=20.9years Mean birth weight=2.80kg	Prospective Cohort	Not applicable	Birth weight in SD-scores; adjusted for age, gender, height, birth length, birth length*adult height: Lumbar spine $\beta = -1.80$, $p = 0.026$ Total body $\beta = -0.38$, $p = 0.471$	Only study to find a negative association between birth weight and BMD; authors propose association mediated by weight gain during childhood as study focused on birth size and adult height

¹NS=non significant

²CI=confidence interval

Table 2. Inclusion rates; UMass Vitamin D Status Study, 2006-2008.

	N(%)
Original Study Sample	186
Missing birth weight	37 (19.9)
Missing DXA	9 (4.8)
Final Study Sample	149 (80.1)

Table 3. Characteristics of included and excluded participants; UMass Vitamin D Status Study, 2006-2008.

Characteristic	Included N(%)	Excluded N(%)	p-value
Age	21.8 (3.4)	20.7 (2.2)	0.19
Height	166.5 (6.2)	166.3 (5.5)	0.97
Weight	64.3 (10.2)	62.3 (8.7)	0.30
Race			
White	128 (85.9)	31 (83.8)	0.72
Other	21 (14.1)	6 (16.2)	

Table 4. Percent distribution of birth weight; UMass Vitamin D Status Study, 2006-2008.

Birth Weight	N(%)
<7.0 lbs.	38 (25.5)
7.0-8.4 lbs.	78 (52.4)
≥8.5 lbs.	33 (22.1)
Total	149 (100)

Table 5. Distribution of covariates according to birth weight; UMass Vitamin D Status Study, 2006-2008.

	Birth Weight			p-value*
	<7.0 lbs. N=38	7.0-8.4 lbs. N=78	≥8.5 lbs. N=33	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	22.9 (4.0)	21.4 (3.1)	21.3 (2.9)	0.05
Height (cm)	164.9 (5.6)	166.5 (6.8)	168.2 (5.1)	0.09
Weight (kg)	62.1 (9.5)	63.6 (10.4)	68.7 (9.7)	0.02
Waist Circumference (cm)	77.3 (8.3)	78.0 (8.9)	82.8 (8.2)	0.01
Calcium (mg/day, energy-adjusted)	1168 (487)	1096 (427)	1133 (392)	0.70
Vitamin D (IU/day, energy-adjusted)	404 (313)	390 (282)	346 (275)	0.67
Dark meat fish (servings/day)	0.08 (0.11)	0.07 (0.12)	0.06 (0.08)	0.58
Physical Activity (MET-hours/week)	53.2 (46.9)	55.9 (49.7)	63.9 (58.8)	0.66
Age at menarche	12.4 (1.4)	12.5 (1.4)	12.4 (1.3)	0.97
	N(%)	N(%)	N(%)	
Race				
White	34 (89.5)	65 (83.3)	29 (87.9)	0.74
Other	4 (10.5)	13 (16.7)	4 (12.1)	
Smoking Status				
Never	31 (81.6)	69 (88.5)	30 (90.9)	0.49
Ever	7 (18.4)	9 (11.5)	3 (9.1)	
Alcohol Use				
Never	2 (6.9)	8 (13.1)	3 (11.1)	0.69
Ever	27 (93.1)	53 (86.9)	24 (88.9)	
Oral Contraceptive Use				
Never	14 (36.8)	38 (48.7)	10 (30.3)	0.24
Past	8 (21.1)	11 (14.1)	10 (30.3)	
Current	16 (42.1)	29 (37.2)	13 (39.4)	

*p-values from analysis of variance for continuous covariates and chi-square or Fisher's Exact tests for categorical covariates.

Table 6. Mean BMC of participants; UMass Vitamin D Status Study, 2006-2008.

	Mean (SD)
BMC (g)	2567.6 (378.1)
	N(%)
BMC<mean	74 (49.7)
BMC≥mean	75 (50.3)

Table 7. Distribution of covariates according to BMC (g); UMass Vitamin D Status Study, 2006-2008.

	Bone Mineral Content		p-value*
	<mean N=74	≥mean N=75	
	Mean (SD)	Mean (SD)	
Age	21.9 (3.6)	21.6 (3.2)	0.66
Height (cm)	162.9 (5.1)	170.0 (5.2)	<0.01
Weight (kg)	58.0 (7.8)	70.6 (8.4)	<0.01
Waist Circumference (cm)	75.6 (8.5)	82.1 (7.9)	<0.01
Calcium (mg/day, energy-adjusted)	1129 (483)	1117 (382)	0.87
Vitamin D (IU/day, energy-adjusted)	393 (311)	375 (263)	0.71
Dark meat fish (servings/day)	0.05 (0.08)	0.10 (0.13)	<0.01
Physical Activity (MET-hours/week)	53.5 (51.0)	60.4 (51.0)	0.41
Age at menarche	12.6 (1.3)	12.3 (1.4)	0.16
	N(%)	N(%)	
Race			
White	60 (81.1)	68 (90.7)	0.09
Other	14 (18.9)	7 (9.3)	
Smoking Status			
Never	62 (83.8)	68 (90.7)	0.21
Ever	12 (16.2)	7 (9.3)	
Alcohol Use			
Never	7 (12.7)	6 (9.7)	0.60
Ever	48 (87.3)	56 (90.3)	
Oral Contraceptive Use			
Never	32 (43.2)	30 (40.0)	0.61
Past	16 (21.6)	13 (17.3)	
Current	26 (35.2)	32 (42.7)	

*p-values from two sample t-tests for continuous covariates and chi-square or Fisher's Exact tests for categorical covariates.

**Table 8. Unadjusted association of birth weight with BMC (g);
UMass Vitamin D Status Study, 2006-2008.**

Birth Weight	Beta Coefficient (SE)	p-value
<7.0 lbs.	ref	
7.0-8.4 lbs.	110.5 (73.2)	0.13
≥8.5 lbs.	257.7 (88.0)	<0.01

Table 9. Unadjusted association of covariates with BMC (g); UMass Vitamin D Status Study, 2006-2008.

	Beta coefficient	Standard Error	p-value
Age	-5.9	9.2	0.52
Height (cm)	40.2	3.8	<0.01
Weight (kg)	26.5	2.1	<0.01
Waist Circumference (cm)	19.4	3.2	<0.01
Calcium (mg/day, energy-adjusted)	-0.1	0.1	0.58
Vitamin D (IU/day, energy-adjusted)	-0.1	0.1	0.65
Dark meat fish (servings/day)	700.1	270.1	0.01
Physical Activity (MET-hours/week)	1.3	0.6	0.03
Age at menarche	-28.7	22.8	0.21
Race			
White	ref		
Other	-30.9	89.3	0.73
Smoking Status			
Never	ref		
Ever	-137.4	92.5	0.14
Alcohol Use			
Never	ref		
Ever	44.0	108.6	0.69
Oral Contraceptive Use			
Never	ref		
Past	-35.8	85.3	0.68
Current	55.5	69.2	0.42

Table 10. Multivariable association of birth weight with BMC (g); UMass Vitamin D Status Study, 2006-2008.

	Beta Coefficient (SE)	p-value
Model not including body size:		
Birth Weight		
<7.0 lbs.	ref	
7.0-8.4 lbs.	119.7 (71.4)	0.10
≥8.5 lbs.	279.6 (86.1)	<0.01
Dark meat fish (servings/day)	774.3 (263.6)	<0.01
Model including body size:		
Birth Weight		
<7.0 lbs.	ref	
7.0-8.4 lbs.	48.9 (43.1)	0.26
≥8.5 lbs.	84.8 (53.5)	0.12
Height (cm)	22.2 (3.7)	<0.01
Weight (kg)	26.7 (4.0)	<0.01
Waist Circumference (cm)	-12.1 (4.1)	<0.01
Age at menarche	-37.5 (13.6)	<0.01
Dark meat fish (servings/day)	395.9 (162.2)	0.02

Table 11. Univariate odds ratios and 95% confidence intervals of BMC (g) by birth weight; UMass Vitamin D Status Study, 2006-2008.

Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	Referent
7.0-8.4 lbs.	0.9	(0.4, 2.0)
≥8.5 lbs.	2.2	(0.9, 5.8)

Table 12. Univariate odds ratios and 95% confidence intervals of BMC (g) by covariates; UMass Vitamin D Status Study, 2006-2008.

	Odds Ratio	95% CI
Age	1.0	(0.9, 1.1)
Height (cm)	1.3	(1.2, 1.5)
Weight (kg)	1.2	(1.1, 1.3)
Waist Circumference (cm)	1.1	(1.1, 1.2)
Calcium (mg/day, energy-adjusted)	1.0	(1.0, 1.0)
Vitamin D (IU/day, energy-adjusted)	1.0	(1.0, 1.0)
Dark meat fish (servings/day)	87.5	(2.5, 3088.3)
Physical Activity (MET-hours/week)	1.0	(1.0, 1.0)
Age at menarche	0.8	(0.7, 1.1)
Race		
White	1.0	ref
Other	0.4	(0.2, 1.2)
Smoking Status		
Never	1.0	ref
Ever	0.5	(0.2, 1.4)
Alcohol Use		
Never	1.0	ref
Ever	1.4	(0.4, 4.3)
Oral Contraceptive Use		
Never	1.0	ref
Past	0.9	(0.4, 2.1)
Current	1.3	(0.6, 2.7)

Table 13. Multivariable odds ratios and 95% confidence intervals of BMC (g) by birth weight; UMass Vitamin D Status Study, 2006-2008.

Model not including body size: ¹		
Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	Referent
7.0-8.4 lbs.	1.0	(0.5, 2.4)
≥8.5 lbs.	2.8	(1.0, 7.7)
Model including body size: ²		
Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	Referent
7.0-8.4 lbs.	0.7	(0.2, 2.4)
≥8.5 lbs.	1.9	(0.4, 8.3)

¹Adjusted for race and dark meat fish consumption (servings/day)

²Adjusted for height (cm), weight (kg), waist circumference (cm), age at menarche, and dark meat fish consumption (servings/day)

**Table 14. Mean BMD of participants; UMass
Vitamin D Status Study, 2006-2008.**

	Mean (SD)
BMD (g/cm ²)	1.16 (0.08)
	N(%)
BMD<mean	71 (47.6)
BMD≥mean	78 (52.4)

Table 15. Distribution of covariates according to BMD (g/cm^2); UMass Vitamin D Status Study, 2006-2008.

	Bone Mineral Density		p-value*
	<mean N=71	\geq mean N=78	
	Mean (SD)	Mean (SD)	
Age	21.6 (3.5)	21.9 (3.3)	0.50
Height (cm)	164.6 (6.0)	168.2 (5.9)	<0.01
Weight (kg)	60.0 (9.3)	68.3 (9.4)	<0.01
Waist Circumference (cm)	76.6 (8.1)	80.9 (9.0)	<0.01
Calcium (mg/day, energy-adjusted)	1131 (503)	1115 (363)	0.82
Vitamin D (IU/day, energy-adjusted)	385 (313)	383 (264)	0.97
Dark meat fish (servings/day)	0.05 (0.08)	0.09 (0.13)	<0.01
Physical Activity (MET-hours/week)	48.9 (41.6)	64.4 (57.5)	0.06
Age at menarche	12.7 (1.4)	12.2 (1.3)	0.02
	N(%)	N(%)	
Race			
White	61 (85.9)	67 (85.9)	0.99
Other	10 (14.1)	11 (14.1)	
Smoking Status			
Never	62 (87.3)	68 (87.2)	0.98
Ever	9 (12.7)	10 (12.8)	
Alcohol Use			
Never	8 (15.7)	5 (7.6)	0.17
Ever	43 (84.3)	61 (92.4)	
Oral Contraceptive Use			
Never	36 (50.7)	26 (33.3)	0.06
Past	14 (19.7)	15 (19.2)	
Current	21 (29.6)	37 (47.4)	

*p-values from two sample t-tests for continuous covariates and chi-square or Fisher's Exact tests for categorical covariates

Table 16. Unadjusted association of birth weight with BMD (g/cm²); UMass Vitamin D Status Study, 2006-2008.

Birth Weight	Beta Coefficient (SE)	p-value
<7.0 lbs.	ref	
7.0-8.4 lbs.	0.02 (0.02)	0.23
≥8.5 lbs.	0.05 (0.02)	0.01

Table 17. Unadjusted association of covariates with BMD (g/cm²); UMass Vitamin D Status Study, 2006-2008.

	Beta coefficient	Standard Error	p-value
Age	0.0006	0.002	0.75
Height (cm)	0.005	0.001	<0.01
Weight (kg)	0.004	0.001	<0.01
Waist Circumference (cm)	0.003	0.001	<0.01
Calcium (mg/day, energy-adjusted)	0.0008	0.000016	0.73
Vitamin D (IU/day, energy-adjusted)	0.00001	0.00002	0.62
Dark meat fish (servings/day)	0.15	0.06	0.02
Physical Activity (MET-hours/week)	0.0004	0.0001	<0.01
Age at menarche	-0.01	0.004	0.01
Race			
White	ref		
Other	0.009	0.02	0.66
Smoking Status			
Never	ref		
Ever	-0.03	0.02	0.10
Alcohol Use			
Never	ref		
Ever	0.02	0.03	0.46
Oral Contraceptive Use			
Never	ref		
Past	0.01	0.02	0.44
Current	0.02	0.02	0.12

Table 18. Multivariable association of birth weight with BMD (g/cm²); UMass Vitamin D Status Study, 2006-2008.

	Beta Coefficient (SE)	p-value
Model not including body size:		
Birth Weight		
<7.0 lbs.	ref	
7.0-8.4 lbs.	0.02 (0.02)	0.17
≥8.5 lbs.	0.05 (0.02)	<0.01
Dark meat fish (servings/week)	0.15 (0.06)	0.01
Physical activity (MET-hours/week)	0.0004 (0.0001)	<0.01
Age at menarche	-0.01 (0.004)	<0.01
Model including body size:		
Birth Weight		
<7.0 lbs.	ref	
7.0-8.4 lbs.	0.01 (0.01)	0.37
≥8.5 lbs.	0.03 (0.02)	0.11
Weight (kg)	0.007 (0.001)	<0.01
Waist Circumference (cm)	-0.004 (0.001)	<0.01
Physical activity (MET-hours/week)	0.0002 (0.0001)	0.01
Age at menarche	-0.01 (0.004)	<0.01

Table 19. Univariate odds ratios and 95% confidence intervals of BMD (g/cm²) by birth weight; UMass Vitamin D Status Study, 2006-2008.

Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	ref
7.0-8.4 lbs.	1.2	(0.5, 2.6)
≥8.5 lbs.	2.8	(1.1, 7.6)

Table 20. Univariate odds ratios and 95% confidence intervals of BMD (g/cm²) by covariates; UMass Vitamin D Status Study, 2006-2008.

	Odds Ratio	95% CI
Height (cm)	1.1	(1.0, 1.2)
Weight (kg)	1.1	(1.1, 1.1)
Waist Circumference (cm)	1.1	(1.0, 1.1)
Calcium (mg, energy-adjusted)	1.0	(1.0, 1.0)
Vitamin D (IU, energy-adjusted)	1.0	(1.0, 1.0)
Dark meat fish	49.4	(1.6, 1569.7)
Physical Activity	1.0	(1.0, 1.0)
Age	1.0	(0.9, 1.1)
Age at menarche	0.8	(0.4, 2.5)
Race		
White	1.0	ref
Other	1.0	(0.4, 2.5)
Smoking Status		
Never	1.0	ref
Ever	1.0	(0.4, 2.7)
Alcohol Use		
Never	1.0	ref
Ever	2.3	(0.7, 7.4)
Oral Contraceptive Use		
Never	1.0	ref
Past	1.5	(0.6, 3.6)
Current	2.4	(1.2, 5.1)

Table 21. Multivariable odds ratio and 95% confidence intervals of BMD (g/cm²) by birth weight; UMass Vitamin D Status Study, 2006-2008.

Model not including body size:¹

Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	Referent
7.0-8.4 lbs.	1.3	(0.6, 2.9)
≥8.5 lbs.	3.4	(1.2, 9.5)

Model including body size:²

Birth weight	Adjusted OR	95%CI
<7.0 lbs.	1.0	Referent
7.0-8.4 lbs.	1.1	(0.5, 2.8)
≥8.5 lbs.	2.7	(0.9, 2.8)

¹Adjusted for age at menarche and dark meat fish consumption (servings/day)

²Adjusted for weight (kg), waist circumference (cm), age at menarche, and dark meat fish consumption (servings/day)

Table 22. Effect modification of the association between birth weight and BMC and BMD by waist circumference; UMass Vitamin D Status Study, 2006-2008

Model	Waist Circumference				
	Birth Weight	<mean N=83		≥mean N=66	
		Beta coefficient (SE)	p-value	Beta coefficient (SE)	p-value
BMC, without body size factors ¹	<7.0 lbs.	ref		ref	
	7.0-8.4 lbs.	57.1 (78.2)	0.47	186.8 (115.9)	0.11
	≥8.5 lbs.	213.4 (110.6)	0.06	207.7 (123.9)	0.10
	p for interaction=0.50				
BMC, with body size factors ²	<7.0 lbs.	ref		ref	
	7.0-8.4 lbs.	28.6 (47.4)	0.55	74.2 (81.8)	0.37
	≥8.5 lbs.	92.3 (68.7)	0.18	80.9 (89.1)	0.37
	p for interaction=0.73				
BMD, without body size factors ³	<7.0 lbs.	ref		ref	
	7.0-8.4 lbs.	0.005 (0.02)	0.79	0.04 (0.03)	0.13
	≥8.5 lbs.	0.05 (0.2)	0.05	0.05 (0.03)	0.10
	p for interaction=0.36				
BMD, with body size factors ⁴	<7.0 lbs.	ref		ref	
	7.0-8.4 lbs.	-0.002 (0.02)	0.91	0.03 (0.02)	0.29
	≥8.5 lbs.	0.03 (0.02)	0.15	0.02 (0.03)	0.41
	p for interaction=0.37				

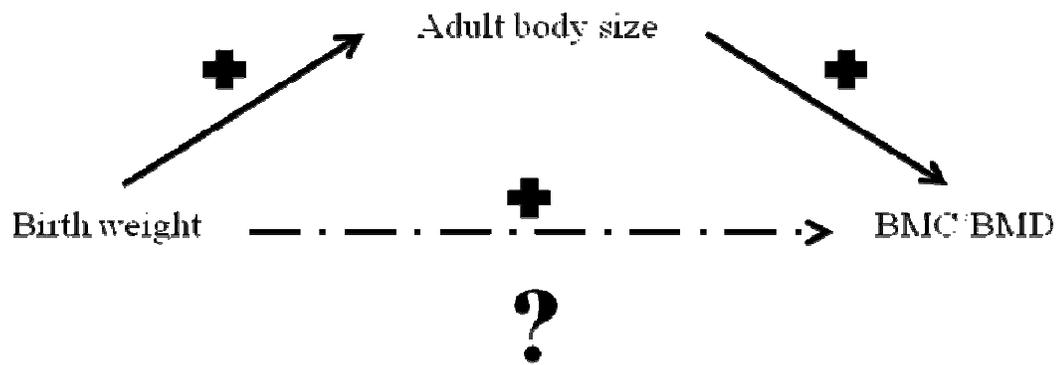
¹ Adjusted for dark meat fish consumption (servings/day)

² Adjusted for height (cm), weight (kg), waist circumference (cm), age at menarche, and dark meat fish consumption (servings/day)

³ Adjusted for dark meat fish consumption (servings/day), physical activity (MET-hours/week), and age at menarche

⁴ Adjusted for weight (kg), waist circumference (cm), physical activity (MET-hours/week), and age at menarche

Figure 1. Potential pathways of association between birth weight and BMC/BMD.



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