Bone 121 (2019) 9–15

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Body composition and bone mineral density in childhood

Lisa B. Rokoff[a,*], Sheryl L. Rifas-Shiman[a], Karen M. Switkowski[a], Jessica G. Young[a], Clifford J. Rosen[b], Emily Oken[a,c], Abby F. Fleisch[d,e]

[a] Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
[b] Center for Clinical and Translational Research, Maine Medical Center Research Institute, Maine Medical Center, Scarborough, ME, USA
[c] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[d] Pediatric Endocrinology and Diabetes, Maine Medical Center, Portland, ME, USA
[e] Center for Outcomes Research and Evaluation, Maine Medical Center Research Institute, Portland, ME, USA

ARTICLE INFO

Keywords:
Adiposity
Body composition
Areal bone mineral density
Dual-energy X-ray absorptiometry

ABSTRACT

Background: Body mass compartments may have different directions of influence on bone accrual. Studies of children are limited by relatively small sample sizes and typically make strong assumptions of linear regression.
Objective: To evaluate associations of overall body mass, components of overall body mass (fat-free and total fat), and components of total fat mass (truncal and non-truncal fat), measured via dual-energy X-ray absorptiometry (DXA) and anthropometry, with total body less head areal bone mineral density (aBMD) Z-score in mid-childhood.
Methods: We performed a cross-sectional study among 876 Boston-area children who had DXA measures. We evaluated linearity of associations using generalized additive models.
Results: Children were median 7.7 (range 6–10) years of age, and 61% were white. After adjustment for sociodemographics and other compartments of body mass, overall body mass, particularly the fat-free mass component, appeared to have a positive relationship with aBMD Z-score [e.g., 0.25 (95% CI: 0.23, 0.28) per 1-kg fat-free mass]. The relationship between truncal fat and aBMD Z-score appeared non-linear, with a negative association only in children with levels of fat mass in the upper 15th percentile [−0.17 (95% CI: −0.26, −0.07) aBMD Z-score per 1-kg truncal fat mass], while non-truncal fat mass was not associated with aBMD Z-score.
Conclusions: Our analyses suggest that central adiposity is associated with lower aBMD Z-score only in children with the highest levels of abdominal fat. This finding raises the possibility of a threshold above which central adipose tissue becomes more metabolically active and thereby adversely impacts bone.

1. Introduction

Peak bone mass, which informs future risk of osteoporosis, is established during childhood and adolescence [1]. Therefore, childhood is a critical life-stage to identify factors such as body mass and fat distribution that may impact bone mineral density (BMD). Understanding the role of body mass and fat distribution on BMD in childhood is increasingly important, as the number of children with overweight or obesity has increased dramatically worldwide over the past few decades [2].

Fat-free mass, primarily comprising muscle (i.e., no fat or bone), has consistently been associated with higher BMD in childhood (as reviewed in [3]), but the relationship between fat mass and BMD is less clear. After accounting for fat-free mass, some studies found greater total fat mass to be associated with higher childhood BMD or bone mineral content (BMC) [4–8], whereas others observed a negative [9–12] or null [13–15] association. Central adiposity in particular could adversely affect bone by producing inflammatory cytokines or exacerbating insulin resistance that may increase bone resorption and impede skeletal development [16,17]. An association between greater central adiposity and lower BMD or BMC has been observed in a limited literature investigating fat distribution and bone density or mass in

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; aBMD, areal bone mineral density; BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; SAT, subcutaneous adipose tissue; SS, subscapular skinfold thickness; TR, triceps skinfold thickness; VAT, visceral adipose tissue

* Corresponding author at: Department of Environmental Health, Harvard T.H. Chan School of Public Health, 401 Park Drive, 4th Floor West, Boston, MA 02215, USA.
E-mail address: lrokoff@mail.harvard.edu (L.B. Rokoff).

https://doi.org/10.1016/j.bone.2018.12.009
Received 11 June 2018; Received in revised form 20 November 2018; Accepted 12 December 2018
Available online 15 December 2018

childhood [17–22]. However, these studies used relatively small or homogenous study populations (i.e., only overweight children), did not examine differences in associations by race/ethnicity, and except for one recent study [12], did not investigate the possibility of non-linear associations between body composition and BMD or BMC. These fragmented and restricted prior observations suggest the need to examine the role of body composition components on BMD in a larger, more generalizable cohort of children.

In the present analysis, we used data from a large Boston-area cohort to examine cross-sectional associations of dual-energy X-ray absorptiometry (DXA) and anthropometric measures of overall body mass, components of overall body mass (fat-free mass and total fat mass), and components of total fat mass (truncal fat mass and non-truncal fat mass) with areal bone mineral density (aBMD) Z-score in mid-childhood. We investigated potential non-linearity and differences in associations by race/ethnicity. We hypothesized that greater overall body mass, particularly the fat-free mass component, would be associated with higher aBMD Z-score, whereas greater central adiposity would be associated with lower aBMD Z-score.

2. Materials and methods

2.1. Study population and design

This study was a cross-sectional analysis of data from Project Viva, a longitudinal cohort study of 2128 mother-infant pairs initially enrolled during pregnancy from Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in the greater-Boston area [23]. Of the 2128 live births, 1116 children participated in a mid-childhood research visit. The present analysis included 876 children who had a DXA scan for measurement of body composition and BMD at the mid-childhood visit [median 7.7 (range 6–10) years of age]. All mothers provided written informed consent, and the study was approved by Institutional Review Boards of participating institutions.

2.2. DXA measurements

We used DXA (Discovery A model; Hologic Inc., Marlborough, MA) to measure fat-free mass, total fat mass, truncal fat mass, and non-truncal (i.e., extremity) fat mass. We calculated overall body mass as fat-free mass + total fat mass. We also used DXA to measure total body less head aBMD (g/cm^2). As compared to regional aBMD measures used for adults, whole body aBMD has less variability during skeletal development and increased reproducibility, so it is preferred for pediatric evaluations. We excluded head mass not only from aBMD but from all body mass measures for consistency between exposure and outcome measures and because the skull is not highly responsive to environmental influences [24]. In the present analysis, we used aBMD rather than BMC, as it is the most commonly-used measure of bone development in pediatric clinical settings and has been shown to track through later childhood and early adulthood [25]. We derived age-, sex-, race-, and height-standardized aBMD Z-scores using U.S. national reference data [26].

We used the same DXA machine on all participants and calibrated it daily with a standard synthetic phantom to check for machine drift. A single, trained investigator checked all scans for positioning, movement, and artifact, and defined body regions for analysis. We analyzed data with pediatric software (Hologic, version 12.6). Intra-rater reliability on a subset of the DXA measurements was high (ICC $>$ 0.91).

2.3. Anthropometric measurements

Trained research staff measured each child's height to the nearest 0.1 cm with a calibrated stadiometer (Shorr Productions, Olney, MD). We measured waist circumference to the nearest 0.1 cm with a Hoechstmass measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Germany). We measured subscapular skinfold thickness (SS) and triceps skinfold thickness (TR) to the nearest 0.1 mm with Holtain calipers (Holtain LTD, Crosswell, UK) and then calculated their sum (SS + TR) for use in analyses.

2.4. Measurement of covariates

Mothers reported their education and race/ethnicity at enrollment and their marital status and household income at the time of the mid-childhood visit. We abstracted child sex from the interview at time of delivery. We collected questionnaire data on child race/ethnicity in early childhood and on physical activity and environmental tobacco smoke exposure at the mid-childhood visit. The mid-childhood questionnaire also included a pubertal development scale [27] which assessed parental report of the child's pubertal development, and a PrimeScreen [23] which assessed the child's diet including frequency of consumption of dairy products, including milk, yogurt, cottage and hard cheeses, butter, and ice cream. We shipped serum aliquots on dry ice to Massachusetts General Hospital (Boston, MA) for serum 25-hydroxyvitamin D [25(OH)D] measurement by an isotope dilution liquid chromatography-tandem mass spectrometry assay, in the subset of participants (n = 577) that provided blood samples.

2.5. Statistical analysis

We examined associations of DXA measures of overall body mass, fat-free mass, total fat mass, truncal fat, and non-truncal fat mass with aBMD Z-score in mid-childhood. We excluded bone mass from measures of overall body mass and fat-free mass to avoid inflated effect estimates as a result of having a component of the outcome (bone mass) included in the exposure.

In primary analyses, we fit three covariate-adjusted penalized spline generalized additive models to examine associations of 1) overall body mass, 2) components of overall body mass (fat-free mass and total fat mass), and 3) components of total fat mass (truncal fat mass and non-truncal fat mass) with aBMD Z-score. In all three models, we included the following covariates potentially associated with body composition and aBMD Z-score [28,29]: maternal marital status (married/lived with partner or not), annual household income ($>$ or $\leq$ \$70,000); child sex, race/ethnicity (white, black, Asian, Hispanic, other), height, and age. In the model of the components of total fat mass, we also adjusted for fat-free mass, which allowed us to assess the effect of an increase in truncal or non-truncal fat mass on aBMD Z-score independent of a compensatory decrease in fat-free mass. We considered additional covariates [maternal education (with or without college degree), pubertal status (continuous scale), physical activity (h/week), environmental tobacco smoke exposure (0 h/week, $<$ 1 h/week, $\geq$ 1 h/week), dairy intake (servings/day), and 25(OH)D plasma concentration] but did not include these in our final models as adjustment did not appreciably change results. We substituted maternal race/ethnicity in the 10% of participants for whom child race/ethnicity data was missing. Ninety-four percent (820 of 876) of participants had complete covariate information.

In the fully-adjusted models, we visually evaluated the linearity of each body composition variable and continuous covariates in relation to aBMD Z-score and included the variable as a smooth (non-linear) term in the models in cases of non-linearity. We visually observed that for each body mass variable non-linearly associated with aBMD Z-score, there were two slopes of association, separated by an approximate threshold. We estimated the threshold to be the 5-unit body mass percentile increment (e.g., 70, 75, 80th percentiles) closest to the slope peak. To quantify the slopes above and below this threshold in cases of non-linearity, we used the respective final model to predict the change in aBMD Z-score over a range of values of body mass near the endpoints of each slope. We then divided the predicted estimate by the difference of these endpoints to obtain an average change in aBMD Z-score per 1-

Table 1
Participant characteristics overall (n = 876)[a] and by quartiles of total body (excluding skull) areal bone mineral density (aBMD) Z-score in mid-childhood.

		Quartiles of aBMD Z-score[b]			
	Overall	Q1	Q2	Q3	Q4
	n = 876	n = 219	n = 219	n = 219	n = 219
	Median (IQR) or %	Median (IQR) or %			
Maternal/household characteristics at mid-childhood					
Married or cohabitating (%)	85	92	85	85	80
Annual household income > $70,000 (%)	72	72	71	77	66
Child characteristics					
Female (%)	51	53	53	48	49
Race/ethnicity (%)					
White	61	64	64	59	56
Black	19	14	19	21	21
Hispanic	5	3	3	4	10
Asian	3	4	1	4	2
Other	13	16	12	12	11
Age (years)	7.7 (1.0)	7.7 (0.7)	7.7 (1.1)	7.7 (1.1)	7.7 (1.1)
Height (cm)	127.5 (9.1)	126.3 (8.9)	127.5 (9.3)	127.8 (9.3)	127.8 (10.2)
aBMD Z-score[b]	−0.88 (1.03)	−1.74 (0.49)	−1.14 (0.25)	−0.61 (0.26)	0.02 (0.53)
Child body mass (kg)[c]					
Overall body mass	23.9 (7.3)	21.4 (5.2)	23.2 (5.9)	24.5 (7.0)	27.2 (9.6)
Components of overall body mass					
Fat-free mass	18.0 (4.8)	16.3 (3.6)	17.7 (4.6)	18.3 (4.6)	20.2 (5.5)
Total fat mass	5.5 (3.6)	4.7 (2.4)	5.4 (2.9)	5.5 (3.5)	7.4 (5.8)
Components of total fat mass					
Truncal fat mass	1.9 (1.4)	1.6 (0.9)	1.9 (1.1)	1.9 (1.4)	2.6 (2.3)
Non-truncal fat mass	3.6 (2.3)	3.1 (1.6)	3.5 (1.9)	3.7 (2.2)	4.7 (3.2)

Abbreviations: aBMD – areal bone mineral density; IQR – interquartile range; Q1–4 – quartiles 1–4.
[a] Missing data in overall cohort: 35 for married/cohabitating; 47 for household income; 2 for child race/ethnicity.
[b] Sex-, age-, race-, and height-standardized total body (excluding skull) aBMD Z-score.
[c] Excluding head mass.

kg increment in body mass. We used a bootstrapping procedure with 10,000 bootstrapped samples to calculate 95% confidence intervals (CIs) around each predicted change in aBMD Z-score. Models for some bootstrap samples failed to converge due to sparse data at the endpoints of the slope, and in these cases, we used a slightly narrower range of body mass endpoints. In sensitivity analyses, we stratified by sex, restricted to pre-pubertal participants [n = 653 (77% of analytic cohort)], and stratified by race/ethnicity for 874 participants with race/ethnicity data available [white (n = 533), black (n = 162), and other (n = 179)].

In secondary analyses of anthropometric measures, we fit two additional covariate-adjusted penalized spline generalized additive models to examine the role of 1) SS + TR (a proxy for total fat mass) and 2) waist circumference (a proxy for truncal fat mass) on aBMD Z-score. We adjusted for the same covariates as in the primary analysis, along with all components of body mass in each model by additionally accounting for DXA-measured fat-free mass in the analysis of SS + TR and DXA-measured fat-free mass and non-truncal fat mass in the analysis of waist circumference. We visually evaluated the linearity of each anthropometric measurement in relation to aBMD Z-score.

We used SAS version 9.4 (Cary, NC) for descriptive analyses and R Statistical Computing version 3.3.2 (R Core Team; Vienna, Austria) for the penalized spline generalized additive models.

3. Results

3.1. Population characteristics

Participants had a median age of 7.7 (interquartile range 1.0) years, and 61% were white. Eighty-five percent of mothers were married or lived with their partner and 72% had a household income above $70,000 (Table 1). As compared to participants who completed the mid-childhood visit but were excluded from this analysis (n = 240), those included (n = 876) were younger, more likely to be a minority race/ethnicity, and more likely to have a lower household income (Supplemental Table 1).

Fat-free mass was moderately correlated with total fat mass (Spearman r = 0.53, $p < 0.05$). Total fat mass was strongly correlated with its components, truncal fat mass (Spearman r = 0.98, $p < 0.05$) and non-truncal fat mass (Spearman r = 0.99, $p < 0.05$) (Supplemental Table 2). When we compared DXA measures with their corresponding anthropometric measures, total fat mass and SS + TR (Spearman r = 0.90, $p < 0.05$) and truncal fat mass and waist circumference (Spearman r = 0.79, $p < 0.05$) were highly correlated (data not shown).

Children with the highest aBMD Z-scores were more likely to be Hispanic or black and live in a lower income household. Mothers of these children were more likely to be unmarried. In addition, children with the highest aBMD Z-scores had higher unadjusted overall body mass, fat-free mass, total fat mass, truncal fat mass, and non-truncal fat mass (Table 1).

3.2. Measures of body composition and aBMD Z-score

In covariate-adjusted analyses, the relationship between DXA overall body mass and aBMD Z-score appeared non-linear with an approximate threshold near the 80th percentile of overall body mass (~30 kg), above which the positive association appeared weaker (Fig. 1). Specifically, we computed a 0.18 increase (95% CI: 0.13, 0.22) in average aBMD Z-score per 1-kg increment in body mass in the range of 12 to 27 kg, whereas we computed a 0.06 increase (95% CI: 0.04,

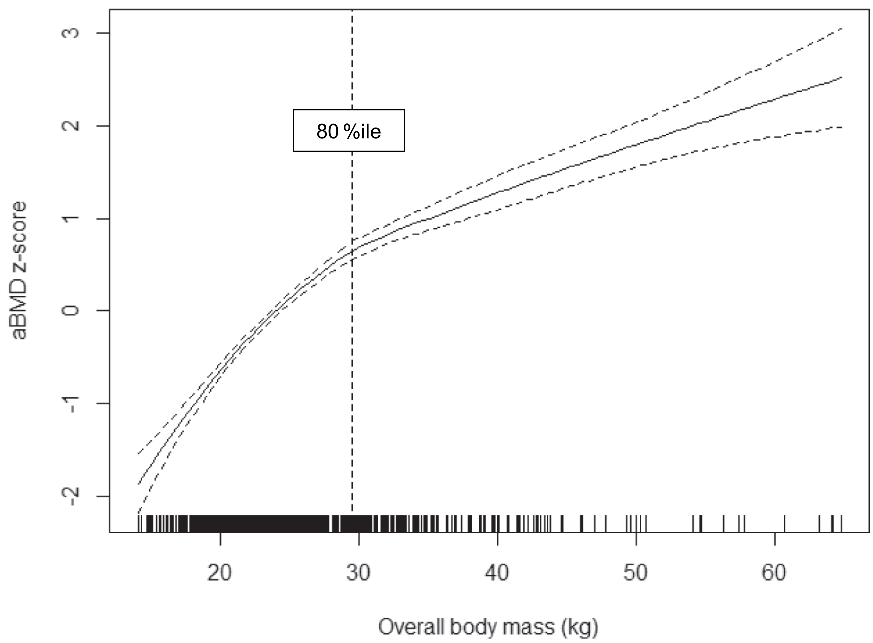

Fig. 1. Association between overall body mass and with sex-, age-, race-, and height-standardized total body (excluding skull) areal bone mineral density (aBMD) Z-score in mid-childhood. See Supplemental Table 3 for predicted effect estimates (95% confidence intervals).

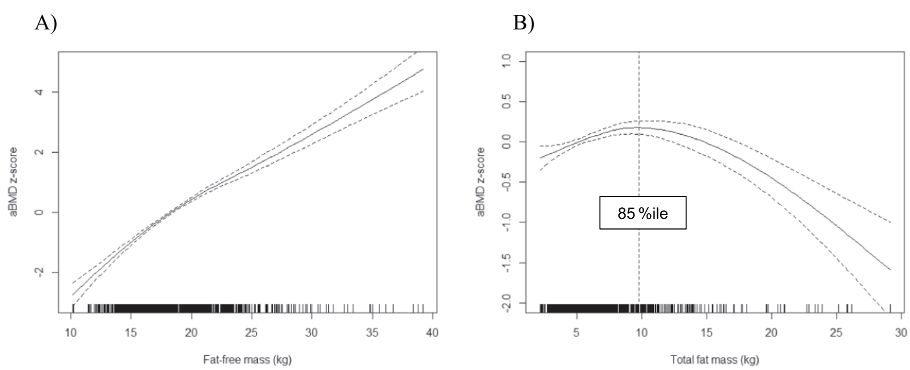

Fig. 2. Associations of components of overall body mass, fat-free mass (panel A) and total fat mass (panel B) with sex-, age-, race-, and height-standardized total body (excluding skull) areal bone mineral density (aBMD) Z-score in mid-childhood. See Supplemental Table 3 for predicted effect estimates (95% confidence intervals).

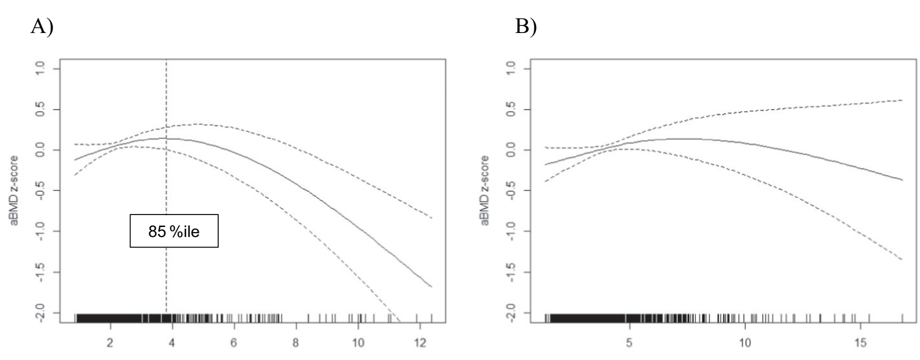

Fig. 3. Associations of components of total fat mass, truncal (panel A) and non-truncal (panel B) fat mass, with sex-, age-, race-, and height-standardized total body (excluding skull) areal bone mineral density (aBMD) Z-score in mid-childhood. See Supplemental Table 3 for predicted effect estimates (95% confidence intervals).

0.08) in average aBMD Z-score per 1-kg increment in body mass in the range of 30 to 45 kg (Supplemental Table 3).

For the components of overall body mass (fat-free mass and total fat mass), the association between fat-free mass and aBMD Z-score appeared linear. For each 1-kg increment in fat-free mass, the average aBMD Z-score was 0.25 higher (95% CI: 0.23, 0.28). The relationship between total fat mass and aBMD Z-score appeared non-linear with an approximate threshold near the 85th percentile of total fat mass (~10 kg), below which the association appeared weakly positive and above which the association appeared negative (Fig. 2). Specifically, below the threshold, we computed a 0.05 increase (95% CI: 0.00, 0.08) in average aBMD Z-score per 1-kg increment in total fat mass in the range of 5 to 9 kg. Above the threshold, we computed a 0.08 decrease (95% CI: –0.11, −0.04) in average aBMD Z-score per 1-kg increment in total fat mass in the range of 15 to 19 kg (Supplemental Table 3).

For the components of total fat mass (truncal fat mass and non-truncal fat mass), there appeared to be no association between non-truncal fat mass and aBMD Z-score. For each 1-kg increment in non-truncal fat mass index, the average aBMD Z-score was 0.02 higher (95% CI: –0.05, 0.08). The relationship between truncal fat mass and aBMD Z-score appeared non-linear, with an approximate threshold near the 85th percentile of truncal fat mass (~4 kg), below which the association appeared null and above which the association appeared negative. Specifically, we computed a 0.08 increase (95% CI: –0.07, 0.20) in average aBMD Z-score per 1-kg increment in truncal fat mass in the range of 1.5 to 3.5 kg, and a 0.17 decrease (95% CI: –0.26, −0.07) in average aBMD Z-score per 1-kg increment in truncal fat mass in the range of 5.5 to 7.5 kg (Fig. 3, Supplemental Table 3).

3.3. Secondary analyses

We found no considerable differences in results after stratification by sex or after restricting to pre-pubertal participants (data not shown). When we stratified by child race/ethnicity, we found no appreciable differences in associations of overall body mass, fat-free mass, and non-truncal mass with aBMD Z-score (data not shown). Total and truncal fat mass had similar patterns of association with aBMD Z-score for all race/ethnicities. However, the threshold above which the association appeared negative occurred at a lower fat mass in black children (e.g., 70th percentile; ~2.6 kg for truncal fat mass) than in white children (e.g., 85th percentile; ~3.7 kg for truncal fat mass) or children of other race/ethnicities (e.g., 90th percentile; ~4.5 kg for truncal fat mass) (Supplemental Figs. 1 and 2). In addition, the negative association between truncal fat mass and aBMD Z-score above the threshold was less pronounced for children who were black as compared to all other race/ethnicities, and confidence intervals were wide for all stratified analyses (Supplemental Table 3).

In analyses of anthropometric measures, results were comparable to the corresponding DXA measures. SS + TR (proxy for total fat mass) appeared non-linearly associated with aBMD Z-score with an approximate threshold near the 90th percentile (~30 mm), below which the association appeared positive and above which it appeared negative. Waist circumference (proxy for truncal fat mass) also appeared non-linearly associated with aBMD Z-score with an approximate threshold near the 90th percentile (~71 cm), below which the association appeared positive and above which it appeared negative (data not shown).

4. Discussion

In our analysis of a large Boston-area cohort, children with greater overall body mass and higher fat-free mass had higher aBMD Z-scores. When holding fat-free mass constant, greater total fat mass was positively associated with aBMD Z-score in children below the 85th percentile of fat mass, whereas greater fat mass was negatively associated with aBMD Z-scores in children above the 85th percentile of fat mass. The association between greater fat mass and lower aBMD Z-scores in children with the most adiposity was driven by their truncal (i.e., abdominal) rather than non-truncal (i.e., extremity) fat depot.

Our observation that greater overall body mass, and fat-free mass in particular, was associated with higher BMD is consistent with a well-established literature, including findings from a recent systematic review in children and adolescents [3] and a meta-analysis in adults [30]. Muscle exerts biomechanical forces on bone that strengthen the skeleton in individuals with greater muscle mass [31]. In addition, aBMD is a two-dimensional measurement integrating overall size, such that larger individuals tend to have higher aBMD.

While the associations of overall body mass and fat-free mass with BMD are well-described, studies of fat mass and BMD or BMC in childhood have shown mixed results, reporting positive [4–8], negative [9–12], or null [13–15] associations. We observed a weakly positive association between fat mass and aBMD Z-score in children with relatively lower levels of fat mass, and a stronger negative association between fat mass and aBMD Z-score in children with relatively higher levels of fat mass. This finding is partly consistent with results from a recent analysis of 8–19 year old children and adolescents in NHANES in which there was a negative association between body fat percentage and BMC only for children with a body fat percentage above the mean [12]. Other prior studies did not evaluate the potential for non-linear associations. Because different study populations may have varying ranges of fat mass, non-linear associations between fat mass and BMD may partly explain the conflicting existing literature. The mixed findings could also be due to differences in fat deposition pattern, which can vary between populations [32,33] and was not considered in most of these prior studies.

Our findings support the idea that the relationship between fat mass and BMD may be influenced by the pattern of fat deposition. We found truncal (i.e., abdominal) fat mass rather than non-truncal (i.e., extremity) fat mass to be responsible for the association between greater fat mass and lower aBMD Z-score. This finding is consistent with a limited existing literature of primarily small cohorts in which the majority [17–22] but not all [15] reported a negative association between abdominal fat mass and BMD or BMC in childhood. It is notable that most of these studies [17–19,21,22] were in overweight cohorts, consistent with our observation of a negative association only in children with the highest levels of fat mass. Our study builds on the existing literature by evaluating non-linear associations between fat deposition and aBMD Z-scores in a larger cohort of children with a wide range of body and fat mass.

Abdominal fat mass comprises both visceral adipose tissue (VAT) that surrounds the internal organs and peritoneal cavity and subcutaneous adipose tissue (SAT) that lies under the abdominal skin. Studies that measured VAT and SAT by single slice computed tomography or magnetic resonance imaging suggest that the association between greater central adiposity and lower BMD or BMC is driven by the visceral component [17–21]. This observation on the influence of central adiposity is not surprising, as visceral adipocytes differ in both origin and function from fat cells in the subcutaneous depot. Visceral fat secretes inflammatory cytokines such as TNF-α and IL-6, which may induce bone resorption and impede skeletal development [16,34]. For example, as compared to normal-weight mice, diet-induced obese mice with high visceral fat mass concurrently exhibited greater levels of inflammatory cytokines and reduced BMD [35]. In addition, free fatty acid secretion from visceral fat may disrupt insulin receptor expression leading to insulin resistance, which may impair osteoblast differentiation, proliferation, and survival and consequently reduce bone acquisition [36]. In vitro studies have shown that insulin signaling in osteoblasts leads to bone remodeling [37], and in an observational study, as compared to healthy adolescents, those with higher insulin resistance had lower bone mass [17]. Thus, greater abdominal fat mass may be associated with lower BMD as a result of cytokine, adipokine, and free fatty acid secretion from VAT, which leads to inflammation and insulin resistance.

Our observation that greater central adiposity was associated with lower aBMD Z-score only in children with the highest levels of abdominal fat mass may be due to a more metabolically active adipose depot in these individuals. Studies of adult cohorts have shown that individuals with the greatest central adiposity have disproportionately higher systemic inflammatory markers, such as C-reactive protein, as compared to those with lower levels of adiposity [38,39]. In addition, individuals with the greatest central adiposity have disproportionately higher levels of insulin resistance [40]. Consistent with this body of research, the association between central adiposity and other adverse outcomes such as atrial fibrillation [41], vascular events [42], and allcause mortality [43], has been shown to be strongest in individuals with the highest levels of central adiposity. Thus, our study adds to a growing body of literature suggesting that there may be a threshold of central adiposity beyond which individuals are more prone to develop metabolically-mediated adverse health outcomes.

We also observed some differences in the association between fat mass and aBMD Z-score among different race/ethnicities. As compared to children who were white or other race/ethnicities, black children had a lower fat mass threshold above which the fat mass-aBMD Z-score association appeared negative. Also, in black children, the association between higher fat mass and lower aBMD Z-score above this threshold was less pronounced. It is possible that the propensity for black individuals to have a higher bone density [44] outweighs negative effects of metabolically active central adipose tissue. However, sample sizes were small and confidence intervals were wide within race/ethnicity strata, suggesting the importance of replication of these results.

Limitations of the present study include the cross-sectional observational study design, which cannot demonstrate causality, and potential unmeasured confounding also impacting causal interpretation. Our study is limited largely to pre-pubertal children (age range: 6–10 years old) and additional studies, including future work in this cohort, will help better characterize associations between body composition and BMD across puberty. Also, while mean aBMD Z-scores in Project Viva are within the normal range, low-normal values likely reflect machine bias [45]. As recommended [45], we used a single DXA machine for all participants to eliminate machine discrepancies as a source of bias in our effect estimates of body composition on aBMD Z-score. Furthermore, overlying fat is a potential source of error in BMD measurements [46–48], and it is possible that our findings fully or partially reflect this phenomenon. Finally, we did not have information on SAT or VAT, lumbar spine BMD, fracture incidence, or other measures of bone strength in our cohort.

Our study has several strengths, including use of the largest population-based cohort to date to examine the association between fat distribution and BMD in childhood. In addition, the study was conducted in a cohort with expansive data on maternal and child health sociodemographic behaviors, which allowed us to evaluate and account for important potential confounders. We also explored whether certain body mass exposures appeared to differ in their relationship with aBMD Z-score based on race/ethnicity. In the present study, our use of primarily pre-pubertal children also minimized potential confounding or mediation by pubertal status. Furthermore, rather than making strong assumptions of linearity for associations between body composition and BMD, we evaluated the possibility of non-linear associations.

In conclusion, children with greater overall body mass and fat-free mass had higher aBMD Z-scores. However, greater central adiposity appeared to be associated with lower aBMD Z-score in children with the highest levels of abdominal fat mass. This study adds to a growing literature suggesting a potential threshold effect of central adiposity in relation to adverse outcomes throughout the lifecourse.

Funding

The authors have received support from the National Institutes of Health (K24HD069408, UG3OD023286, K23ES024803, and R01HD034568).

Declarations of interest

The authors have nothing to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2018.12.009.

References

[1] L.K. Bachrach, Acquisition of optimal bone mass in childhood and adolescence, Trends Endocrinol. Metab. 12 (1) (2001) 22–28.
[2] M.K. Crocker, J.A. Yanovski, Pediatric obesity: etiology and treatment, Pediatr. Clin. N. Am. 58 (5) (2011) 1217–1240 (xi).
[3] I. Sioen, E. Lust, S. De Henauw, L.A. Moreno, D. Jimenez-Pavon, Associations between body composition and bone health in children and adolescents: a systematic review, Calcif. Tissue Int. 99 (6) (2016) 557–577.
[4] R.P. El Hage, D. Courteix, C.L. Benhamou, C. Jacob, C. Jaffre, Relative importance of lean and fat mass on bone mineral density in a group of adolescent girls and boys, Eur. J. Appl. Physiol. 105 (5) (2009) 759–764.
[5] K. Ka, M.C. Rousseau, M. Lambert, J. O'Loughlin, M. Henderson, A. Tremblay, N. Alos, B. Nicolau, Association between lean and fat mass and indicators of bone health in prepubertal Caucasian children, Horm. Res. Paediatr. 80 (3) (2013) 154–162.
[6] Z.A. Cole, N.C. Harvey, M. Kim, G. Ntani, S.M. Robinson, H.M. Inskip, K.M. Godfrey, C. Cooper, E.M. Dennison, Increased fat mass is associated with increased bone size but reduced volumetric density in pre pubertal children, Bone 50 (2) (2012) 562–567.
[7] M. Jeddi, M.H. Dabbaghmanesh, G. Ranjbar Omrani, S.M. Ayatollahi, Z. Bagheri, M. Bakhshayeshkaram, Relative importance of lean and fat mass on bone mineral density in Iranian children and adolescents, Int. J. Endocrinol. Metab. 13 (3) (2015) e25542.
[8] S. Soininen, V. Sidoroff, V. Lindi, A. Mahonen, L. Kroger, H. Kroger, J. Jaaskelainen, M. Atalay, D.E. Laaksonen, T. Laitinen, T.A. Lakka, Body fat mass, lean body mass and associated biomarkers as determinants of bone mineral density in children 6-8years of age - the physical activity and nutrition in children (PANIC) study, Bone 108 (2018) 106–114.
[9] L. Gracia-Marco, F.B. Ortega, D. Jimenez-Pavon, G. Rodriguez, M.J. Castillo, G. Vicente-Rodriguez, L.A. Moreno, Adiposity and bone health in Spanish adolescents. The HELENA study, Osteoporos. Int. 23 (3) (2012) 937–947.
[10] C. Gallego Suarez, B.H. Singer, A. Gebremariam, J.M. Lee, K. Singer, The relationship between adiposity and bone density in U.S. children and adolescents, PLoS One 12 (7) (2017) e0181587.
[11] H.E. Wey, T.L. Binkley, T.M. Beare, C.L. Wey, B.L. Specker, Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children, J. Clin. Endocrinol. Metab. 96 (1) (2011) 106–114.
[12] I. Duran, K. Martakis, S. Hamacher, C. Stark, O. Semler, E. Schoenau, Are there effects of age, gender, height, and body fat on the functional muscle-bone unit in children and adults? Osteoporos. Int. 29 (5) (2018) 1069–1079, https://doi.org/10.1007/s00198-018-4401-4.
[13] R. El Hage, E. Moussa, C. Jacob, Bone mineral content and density in obese, overweight, and normal-weighted sedentary adolescent girls, J. Adolesc. Health 47 (6) (2010) 591–595.
[14] K.A. Witzke, C.M. Snow, Lean body mass and leg power best predict bone mineral density in adolescent girls, Med. Sci. Sports Exerc. 31 (11) (1999) 1558–1563.
[15] H.C. Jeon, K. Lee, J. Kim, T.J. Park, D.W. Kang, D.J. Park, The relationship between body fat percent and bone mineral density in Korean adolescents: the fifth Korea National Health and nutrition examination survey (KNHANES V-1), 2010, Korean J. Fam. Med. 35 (6) (2014) 303–308.
[16] J.J. Cao, Effects of obesity on bone metabolism, J. Orthop. Surg. Res. 6 (1) (2011) 30.
[17] N.K. Pollock, P.J. Bernard, B. Gutin, C.L. Davis, H. Zhu, Y. Dong, Adolescent obesity, bone mass, and cardiometabolic risk factors, J. Pediatr. 158 (5) (2011) 727–734.
[18] M. Russell, N. Mendes, K.K. Miller, C.J. Rosen, H. Lee, A. Klibanski, M. Misra, Visceral fat is a negative predictor of bone density measures in obese adolescent girls, J. Clin. Endocrinol. Metab. 95 (3) (2010) 1247–1255.
[19] N.K. Pollock, P.J. Bernard, K. Wenger, S. Misra, B.A. Gower, J.D. Allison, H. Zhu, C.L. Davis, Lower bone mass in prepubertal overweight children with prediabetes, J. Bone Miner. Res. 25 (12) (2010) 2760–2769.
[20] A. Afghani, M.I. Goran, Racial differences in the association of subcutaneous and visceral fat on bone mineral content in prepubertal children, Calcif. Tissue Int. 79 (6) (2006) 383–388.
[21] A. Afghani, M.I. Goran, The interrelationships between abdominal adiposity, leptin and bone mineral content in overweight Latino children, Horm. Res. 72 (2) (2009) 82–87.
[22] I.F. Junior, J.R. Cardoso, D.G. Christofaro, J.S. Codogno, A.C. de Moraes, R.A. Fernandes, The relationship between visceral fat thickness and bone mineral density in sedentary obese children and adolescents, BMC Pediatr. 13 (2013) 37.
[23] E. Oken, A.A. Baccarelli, D.R. Gold, K.P. Kleinman, A.A. Litonjua, D. De Meo, J.W. Rich-Edwards, S.L. Rifas-Shiman, S. Sagiv, E.M. Taveras, S.T. Weiss, M.B. Belfort, H.H. Burris, C.A. Camargo Jr., S.Y. Huh, C. Mantzoros, M.G. Parker, M.W. Gillman, Cohort profile: project viva, Int. J. Epidemiol. 44 (1) (2015) 37–48.
[24] N.J. Crabtree, A. Arabi, L.K. Bachrach, M. Fewtrell, G. El-Hajj Fuleihan, H.H. Kecskemethy, M. Jaworski, C.M. Gordon, Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD pediatric official positions, J. Clin. Densitom. 17 (2) (2014) 225–242.
[25] T.A. Wren, H.J. Kalkwarf, B.S. Zemel, J.M. Lappe, S. Oberfield, J.A. Shepherd, K.K. Winer, V. Gilsanz, Longitudinal tracking of dual-energy X-ray absorptiometry bone measures over 6 years in children and adolescents: persistence of low bone mass to maturity, J. Pediatr. 164 (6) (2014) 1280-5.e2.
[26] B.S. Zemel, H.J. Kalkwarf, V. Gilsanz, J.M. Lappe, S. Oberfield, J.A. Shepherd, M.M. Frederick, X. Huang, M. Lu, S. Mahboubi, T. Hangartner, K.K. Winer, Revised

reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study, J. Clin. Endocrinol. Metab. 96 (10) (2011) 3160–3169.
[27] A.F. Fleisch, S.L. Rifas-Shiman, A.M. Mora, A.M. Calafat, X. Ye, H. Luttmann-Gibson, M.W. Gillman, E. Oken, S.K. Sagiv, Early-life exposure to perfluoroalkyl substances and childhood metabolic function, Environ. Health Perspect. 125 (3) (2017) 481–487.
[28] K.K. Davison, L.L. Birch, Childhood overweight: a contextual model and recommendations for future research, Obes. Rev. 2 (3) (2001) 159–171.
[29] H.J. Kalkwarf, B.S. Zemel, V. Gilsanz, J.M. Lappe, M. Horlick, S. Oberfield, S. Mahboubi, B. Fan, M.M. Frederick, K. Winer, J.A. Shepherd, The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race, J. Clin. Endocrinol. Metab. 92 (6) (2007) 2087–2099.
[30] L.T. Ho-Pham, U.D. Nguyen, T.V. Nguyen, Association between lean mass, fat mass, and bone mineral density: a meta-analysis, J. Clin. Endocrinol. Metab. 99 (1) (2014) 30–38.
[31] O. Fricke, E. Schoenau, The 'functional muscle-bone unit': probing the relevance of mechanical signals for bone development in children and adolescents, Growth Hormon. IGF Res. 17 (1) (2007) 1–9.
[32] Q. He, M. Horlick, J. Thornton, J. Wang, R.N. Pierson Jr., S. Heshka, D. Gallagher, Sex and race differences in fat distribution among Asian, African-American, and Caucasian prepubertal children, J. Clin. Endocrinol. Metab. 87 (5) (2002) 2164–2170.
[33] J.C. Chan, V. Malik, W. Jia, T. Kadowaki, C.S. Yajnik, K.H. Yoon, F.B. Hu, Diabetes in Asia: epidemiology, risk factors, and pathophysiology, JAMA 301 (20) (2009) 2129–2140.
[34] N.K. Pollock, Childhood obesity, bone development, and cardiometabolic risk factors, Mol. Cell. Endocrinol. 410 (2015) 52–63.
[35] G.V. Halade, M.M. Rahman, P.J. Williams, G. Fernandes, High fat diet-induced animal model of age-associated obesity and osteoporosis, J. Nutr. Biochem. 21 (12) (2010) 1162–1169.
[36] K. Fulzele, R.C. Riddle, D.J. Digirolamo, X. Cao, C. Wan, D. Chen, M.C. Faugere, S. Aja, M.A. Hussain, J.C. Bruning, T.L. Clemens, Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition, Cell 142 (2) (2010) 309–319.
[37] M. Ferron, J. Wei, T. Yoshizawa, A. Del Fattore, R.A. Depinho, A. Teti, P. Ducy, G. Karsenty, Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism, Cell 142 (2) (2010) 296–308.
[38] A. Khera, G.L. Vega, S.R. Das, C. Ayers, D.K. McGuire, S.M. Grundy, J.A. de Lemos, Sex differences in the relationship between C-reactive protein and body fat, J. Clin. Endocrinol. Metab. 94 (9) (2009) 3251–3258.
[39] B. Thorand, J. Baumert, A. Doring, C. Herder, H. Kolb, W. Rathmann, G. Giani, W. Koenig, Sex differences in the relation of body composition to markers of inflammation, Atherosclerosis 184 (1) (2006) 216–224.
[40] S.R. Preis, J.M. Massaro, S.J. Robins, U. Hoffmann, R.S. Vasan, T. Irlbeck, J.B. Meigs, P. Sutherland, R.B. D'Agostino, Sr, C.J. O'Donnell, C.S. Fox, Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study, Obesity (Silver Spring) 18 (11) (2010) 2191–2198.
[41] Y.S. Baek, P.S. Yang, T.H. Kim, J.S. Uhm, J. Park, H.N. Pak, M.H. Lee, B. Joung, Associations of abdominal obesity and new-onset atrial fibrillation in the general population, J. Am. Heart Assoc. 6 (6) (2017).
[42] N.E.M. Jaspers, J.A.N. Dorresteijn, Y. van der Graaf, J. Westerink, L.J. Kappelle, H.M. Nathoe, A. Algra, F.L.J. Visseren, Relation between adiposity and vascular events, malignancy and mortality in patients with stable cerebrovascular disease, Int. J. Obes. 41 (12) (2017) 1775–1781.
[43] A. Koster, M.F. Leitzmann, A. Schatzkin, T. Mouw, K.F. Adams, J.T. van Eijk, A.R. Hollenbeck, T.B. Harris, Waist circumference and mortality, Am. J. Epidemiol. 167 (12) (2008) 1465–1475.
[44] O.M. Gutierrez, Recent insights into racial differences in bone and mineral metabolism, Curr. Opin. Endocrinol. Diabetes Obes. 18 (6) (2011) 347–351.
[45] R.A. Brownbill, J.Z. Ilich, Measuring body composition in overweight individuals by dual energy x-ray absorptiometry, BMC Med. Imaging 5 (1) (2005) 1.
[46] P. Tothill, D.W. Pye, Errors due to non-uniform distribution of fat in dual X-ray absorptiometry of the lumbar spine, Br. J. Radiol. 65 (777) (1992) 807–813.
[47] P. Tothill, N. Weir, J. Loveland, Errors in dual-energy X-ray scanning of the hip because of nonuniform fat distribution, J. Clin. Densitom. 17 (1) (2014) 91–96.
[48] O.L. Svendsen, C. Hassager, V. Skodt, C. Christiansen, Impact of soft tissue on in vivo accuracy of bone mineral measurements in the spine, hip, and forearm: a human cadaver study, J. Bone Miner. Res. 10 (6) (1995) 868–873.