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Maternal and child factors associated with bone length traits in children at 3 years of age☆

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ABSTRACT

Background: Exposure to sub-optimal maternal vitamin D status during pregnancy has been linked to inadequate in utero bone growth with potential for post-natal deficits, but reported findings are inconsistent. Possible reasons include measurement error in assessing bone length/height, or lack of adjustment for confounding variables such as maternal/infant diet, physical activity and season of birth. The objective of this study was to determine the maternal and child factors associated with bone length traits in children at 3 years of age as part of a longitudinal follow-up of a pregnancy cohort.

Methods: Mother-child dyads enrolled in the Family Atherosclerosis Monitoring In early Life study were included. Maternal serum 25-hydroxyvitamin D (25(OH)D) concentration was measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). Anthropometry, physical activity by questionnaire and dietary assessment by food frequency questionnaire were completed for mothers during pregnancy (27–40 weeks gestation) and for children at 3 years with diet by 3-day food records (Nutritionist Pro). Whole body bone mineral density in mother and child (n = 473) was measured by dual-energy absorptiometry (DXA) at the 3 year visit. A software program was developed using MATLAB to derive bone length measurements from whole body DXA images using 8 long bones of each child. Association between maternal and child variables with offspring bone length was assessed using unadjusted and adjusted multivariate linear regression analyses.

Results: In the final adjusted multivariate regression model, factors associated with child bone length were maternal height (p = 0.05), child birth length (p = 0.005) and child weight z-score at 3 years (p < 0.001). No association was observed between maternal serum 25(OH)D concentrations in pregnancy (of which 77% were in normal range) and child bone length.

Conclusion: In healthy Canadian mothers and their children, the factors associated with child bone length achieved at 3 years of age appear to be related to genetic traits rather than environmental exposures. Measures of the length of long bones in children using DXA scans may have provided a more accurate assessment of bone length than whole body height measures.

1. Introduction

Evidence exists that environmental factors during critical periods of development, such as in utero, have a persistent and significant impact on metabolic structure and function. The hypothesis of the developmental origins of health and disease is that exposures related to maternal and offspring health status play a role in optimizing bone growth in utero and in early life that can impart a lasting impact on bone health in childhood and beyond. Modifiable maternal factors in pregnancy linked to fetal and infant bone health include maternal smoking status [1], vitamin D status [2], pre-pregnancy body mass index (BMI) and gestational weight gain [3], and physical activity [4]. Modifiable dietary factors include maternal protein, calcium [5], vitamin D [6], and alcohol intake [3]. Modifiable childhood health habits include

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childhood dietary calcium [7], protein [8] and vitamin D intake [9], duration of breastfeeding [10], exposure to ultraviolet light [11], as well as childhood physical activity [12].

Due to vitamin D's critical role in bone metabolism, it is an exposure variable of interest in assessing bone health outcomes, particularly in utero [2,13–18]. In a systematic review that addressed vitamin D supplementation and status in pregnancy in relation to maternal and child health outcomes, a meta-analysis of 12 observational studies supported a positive relationship between maternal vitamin D status and offspring bone mass but not birth length [6]. Other epidemiological evidence exists that both supports and refutes an association between maternal 25-dihydroxyvitamin D (25(OH)D) concentrations during pregnancy and childhood long bone growth indicators such as crown-heel length [19], crown-rump length [20], forearm length [21], lower limb length [22], as well as measures of fetal femur and humerus bone length by ultrasound. In these studies, bone outcomes were measured at a variety of ages (between 19 weeks gestation to 9.9 years of age) and by different methods of ultrasound or anthropometry with a stadiometer or length board. Further, the relationship between maternal 25(OH)D concentrations and long bone length between 2 and 9 years of age is not extensively researched, especially in healthy developed country populations.

Bone length has been shown to be a more sensitive measure than body height due to measurement errors inherent in more indirect measures of limb length such as children's supine, standing or sitting height [23]. Our study addressed the issue of measurement bias through the development of a novel software to measure long bone length from a dual-energy absorptiometry (DXA) scan as described in the methods. Decomposing body length into limb length is useful to assess general health and growth. Specifically, using relative leg length has been reported as a reliable indicator of the nutrition and environment quality during infancy and childhood, as fast growing bones like legs are most affected by nutrient deprivation [24].

The primary objective of this study was to determine the inherited and environmental maternal and child factors associated with bone length traits (i.e. sum of all eight bone lengths as the primary outcome) in the children at 3 years of age. DXA scan-derived length measures were obtained from a novel MATLAB program and used to evaluate associations between maternal and child health variables and long bone length in children at 3 years of age. The secondary objective was to evaluate the association of children's bone mineral content (BMC) z-score, total BMC, and child whole body minus the head BMC with the variables found associated with children's bone length traits in the primary analysis.

2. Materials and methods

The study of vitamin D status in pregnancy and bone health in offspring was a sub-study separately funded from the core study called the Family Atherosclerosis Monitoring In early Life (FAMILY) study [25]. For this ancillary study on vitamin D status and determinants of bone health in the mother and child, additional funding from the Dairy Farmers of Canada was obtained and separate ethics approval was granted from the Research Ethics Board at Hamilton Health Sciences/McMaster University. Participants gave informed written consent for this sub-study.

Participants were recruited in the third trimester of pregnancy and data on maternal demographics and lifestyle factors during pregnancy were assessed via questionnaires completed at the initial visit between 27 and 40 weeks gestation. Specifically, maternal physical activity and diet in pregnancy including smoking status and alcohol intake, were assessed by a validated questionnaire [26] and a food frequency questionnaire [26], respectively. The food frequency questionnaire assessed food and supplements consumption over the past 12 months, and was designed to assess vitamin D, calcium, and protein intake in a similar population. Maternal height was measured using a stadiometer, and weight by an electronic scale [25]. Maternal 25(OH)D concentrations at 27–40 weeks gestation was measured in fasted serum samples by liquid chromatography tandem mass spectrometry (LC-MS/MS) using a Waters AQUITY Tandem Quadropole Detector coupled to an AQUITY UPLC system (Waters Corporation), after extraction that includes a saponification step [27] and use of the National Institute of Standards and Technology (NIST) SRM972 standard (National Bureau of Standards, Washington, DC [28]). The inter-assay coefficient of variation (CV) for low samples was 13%, and for high samples was 7%, based on pooled blood samples with approximately 30–80 nM 25(OH)D, with or without spiking with 120 nM of 25(OH)D, respectively. At the 3 year visit, the mother's bone mass was assessed by DXA (QDR®4500 series Hologic Inc. Discovery™ DXA machine, Waltham, MA, Adult whole body software version 12.3.1). The CVs for BMC, bone mineral density (BMD) and body area (BA) were 0.651%, 0.376%, and 0.491% respectively, and maternal whole body BMD z-scores were calculated using reference data embedded in the Hologic software for analysis.

The child's diet was assessed at 3 years of age using a 3-day diet record completed by the parents, and analyzed by Nutritionist Pro Software (Axxya Systems, Stafford, Texas). Supplement intake was assessed by questionnaire. The physical activity of the child was recorded using a modified questionnaire [29]. The child's BMC was assessed in supine position by DXA (QDR®4500 series Hologic Inc. Discovery™ DXA machine, Waltham, MA, Pediatric software). The CVs for BMC, BMD and BA, respectively, were 0.651%, 0.376%, and 0.491% at 3 years of age. If considerable movement was seen in one limb but not the other, the well-captured limb was used as a surrogate as validated by our group [30]. Any scans with unsalvageable distortions due to movement were discarded. Child z-scores were calculated using data from an age- and sex-specific standard curve from the Baylor College of Medicine Body Composition Laboratory Z-score calculator, developed in the Children's Nutrition Research Centre in Texas [31,32].

The child's bone length was extracted from the DXA scan for the 8 long bones of the body (left and right humerus, ulna, femur and tibia). A method using MATLAB software (developed in-house) allowed the measurement of limb lengths by indicating the extremities of each bone on the DXA scans image. The endpoint coordinates in image space for each bone are located using a computer mouse and the coordinates converted into a length value by scaling by the x and y pixel size scaling factors. From a subset of 90 children at 3 years, the intra- and inter-CVs for measurements performed on nine different days were found to be 1% and 2% respectively. These eight bones length measures were the outcome of interest.

Statistical analysis was performed using Statistical Analysis Software (SAS) Version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were computed by calculating the means and standard deviations for normal continuous data; medians and quartiles (Q1 and Q3) for non-normal continuous data; and counts and percentages for categorical data. The strength of the associations between child bone length with known determinants of infant growth, including child birth weight, birth length, dietary intakes, weekly physical activity, season of birth and length of breastfeeding as well as maternal height, smoking status, maternal serum 25(OH)D concentrations, maternal physical activity, and alcohol intake was evaluated. To determine what factors were associated with children's bone traits at 3 years, we conducted a multivariate linear regression analysis using the eight different bone length measures as the bone trait outcomes. A hierarchical modelling approach was conducted by first assessing each factor individually using unadjusted models. Wilks' Lambda, a global test of significance across all 8 bone length outcomes, was used to determine how well each maternal and child health variable contributed to the multivariate model. A p value of < 0.05 was used to determine if a variable was statistically significant. Variables found significant in the unadjusted analyses were then assessed for pair-wise collinearity using a matrix of Pearson's correlation coefficients. These variables were further assessed using the variance inflation factor (VIF). A VIF of

Table 1
Demographic characteristics of participants included in the analysis. Categorical variables are presented as count (percentage), and continuous variables are presented as mean (standard deviation (SD)).

Demographic characteristics	Descriptive statistic (n = 473)
Age (years)	32.4 (4.7)
Ethnicity	
European descent	412 (87.1)
Other	61 (12.9)
Education	
Without high school diploma	30 (6.4)
High school diploma/post-secondary education	442 (93.6)
Missing	1
Household income group (CAN $)	
< $49,999	93 (21.1)
> $50,000–$69,999	64 (14.5)
> $70,000–99,999	116 (26.3)
> $100,000	168 (38.1)
Missing	32
Pre-pregnancy BMI (kg/m^2)	26.5 (6.0)
Missing	38

greater than or equal to 10 indicates a high collinearity issue within the data. If factors were highly-collinear, one was removed while the other was included. The remaining significant factors were then added to a final adjusted multivariate linear regression model. For the adjusted multivariate regression analysis, non-standardized regression coefficients (β) and their corresponding 95% confidence intervals (CIs) and p values are also reported for each of the 8 bone outcomes and factors explored. We repeated this statistical approach for the outcomes Child BMC z-score, Child total body BMC, and Child total body minus the head BMC, where the adjusted linear regression models were adjusted for the significant factors identified from the primary multivariate analysis of 8 bone lengths.

3. Results

A total of 473 participants recruited as part of the FAMILY study were included in the present analysis if the infants were born at term (premature infants excluded) and whole body DXA scans were available for both mother and child (Table 1). The participants were on average 32 years old, and mostly of European descent. They were of high education status with two thirds having household incomes greater than $70,000. The mean pre-pregnancy BMI of this cohort was classified as overweight according to the Health Canada definitions [33].

The majority (76.5%) of participants had adequate vitamin D status (serum 25(OH)D > 50 nmol/L) in the third trimester, and only 5.3% of participants were classified as vitamin D deficient (serum 25(OH)D < 30 nmol/L). Most participants were non-smokers, consumed limited amounts of alcohol, and were mildly physically active (Table 2).

Mothers and their offspring were consuming adequate intakes of calcium and vitamin D, with the exception of children who did not meet the Estimated Average Requirement (EAR) for vitamin D at 3 years of age (Table 3).

At 3 years of age, male infants were significantly taller and heavier than their female counterparts with mean weight of 15.1 kg and 14.6 kg (p = 0.001) and mean height of 96.5 cm and 95.1 cm (p = 0.003). However, when expressed as z-scores using an age- and sex-matched reference population weight and height were similar between sexes. At 3 years of age, DXA scans were successfully completed in 473 children. Of these 473 children, 357 had viable DXA measurements for all 8 bones. The missing or excluded scans were predominantly due to unsolvable movement artifacts in one or more bones. The bone traits for the combined group are detailed in Table 4. There were no differences in the maternal and child characteristics between children with (N = 357) and without (N = 116) bone length measures.

Table 2
Lifestyle characteristics of participants. Categorical variables are presented as n (%), and continuous variables are presented as mean (SD).

Maternal characteristics	Descriptive statistic (n = 473)
25(OH)D (nmol/L)	76.3 (32.7)
Smoking status	
Never smoked	309 (65.9)
Former smoker	144 (30.7)
Smoked during pregnancy	16 (3.4)
Missing	4
Alcohol intake (servings/day)	
0 drink	145 (33.3)
≤1 drink	283 (65.1)
> 1 drink	7 (1.6)
Missing	38
Physical activity	
Sedentary	65 (13.8)
Mildly active	305 (64.6)
Active	69 (14.6)
Very active	33 (7.0)
Missing	1

Table 3
Nutrient intake of mothers and children. Values are expressed as median (Q1, Q3) in reference to Dietary Reference Intakes (DRI; [34]). DRIs are estimated energy requirement (EER) for energy, and estimated average requirement (EAR) for protein, calcium and vitamin D.

Nutrient intake	Mother (27–40 week pregnancy) n = 434		Child (3 year old) n = 313	
	Intake	DRI	Intake	DRI
Energy (kcal/d)	2070 (1568, 2704)	2855[a]	1326 (1143, 1569)	1742 male[c] 1642 female[c]
Protein (g/day)	86 (64, 113)	65[b]	53 (44, 65)	13[d]
Calcium (mg/day)	1338 (915, 1812)	800	832 (651, 1085)	500
Vitamin D (IU/day)	379 (313, 529)	400	192 (124, 281)	400

[a] Based on age, an active physical activity level, and the reference heights and weights for women in the 3rd trimester.
[b] Based on reference weight and recommended protein intake per kilogram for mothers during the 3rd trimester.
[c] Based on age, an active physical activity level, and the reference heights and weights.
[d] Based on reference weight and recommended protein intake per kilogram for 3 year old children.

Table 4
Children's bone traits (n = 357). Data are presented as median (Q1, Q3) for the 4 long bones, for the left and right body side.

Children's bone traits	Length (cm)
Humerus	
Left side	15.34 (14.80, 15.97)
Right side	15.44 (14.71, 15.99)
Ulna	
Left side	12.30 (11.79, 12.77)
Right side	12.26 (11.85, 12.78)
Femur	
Left side	22.79 (21.85, 23.48)
Right side	22.78 (21.84, 23.60)
Tibia	
Left side	18.34 (17.68, 19.06)
Right side	18.28 (17.59, 18.96)

Neither maternal serum 25(OH)D concentrations (unadjusted analysis, across all 8 lengths, p = 0.159) nor maternal vitamin D intake (unadjusted analysis, across all 8 lengths, p = 0.105) in the third trimester of pregnancy were associated with child long bone (across all 8

Table 5
Associations between maternal and child health variables and child bone lengths at 3 years of age. The following variables were not significant in the univariable analysis: maternal serum 25(OH)D concentrations, pre-pregnancy BMI, maternal total vitamin D intake, maternal total calcium intake, maternal total protein intake, maternal milk intake, maternal smoking status, maternal physical activity score, maternal alcohol intake, maternal bone mineral density z-score, maternal gestational weight gain, duration of breastfeeding, season of birth, child protein, child vitamin D intake and child weekend physical activity.

Factors	Left humerus	Right humerus	Left ulna	Right ulna	Left femur	Right femur	Left tibia	Right tibia	Adjusted multivariate linear analysis (across all 8 bone lengths)
	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	β (95% CI) *p*-value	*p*
Maternal height (cm)	0.02 (0.01, 0.04) 0.009	0.02 (0.01, 0.04) 0.009	0.02 (0, 0.03) 0.016	0.01 (0, 0.02) 0.088	0.02 (0, 0.04) 0.048	0.02 (0, 0.04) 0.128	0.03 (0.01, 0.05) 0.002	0.02 (0, 0.04) 0.016	0.046
Infant birth weight (per kg)	−0.08 (−0.39, 0.24) 0.631	−0.08 (−0.40, 0.25) 0.635	−0.15 (−0.41, 0.10) 0.24	−0.14 (−0.39, 0.11) 0.261	−0.40 (−0.82, 0.03) 0.069	−0.47 (−0.89, −0.04) 0.031	−0.18 (−0.54, 0.17) 0.303	−0.12 (−0.46, 0.22) 0.491	0.640
Infant birth length (cm)	0.05 (−0.02, 0.12) 0.177	0.04 (−0.04, 0.11) 0.305	0.08 (0.02, 0.14) 0.005	0.10 (0.05, 0.16) < 0.001	0.18 (0.08, 0.27) < 0.001	0.18 (0.09, 0.28) < 0.001	0.09 (0.01, 0.17) 0.023	0.08 (0, 0.15) 0.055	0.005
Child weight Z-score at 3 years	0.43 (0.32, 0.55) < 0.001	0.43 (0.31, 0.55) < 0.001	0.40 (0.31, 0.49) < 0.001	0.36 (0.27, 0.45) < 0.001	0.58 (0.42, 0.73) < 0.001	0.62 (0.46, 0.77) < 0.001	0.58 (0.46, 0.71) < 0.001	0.60 (0.48, 0.73) < 0.001	< 0.001
Child calcium intake at 3 years (per 100 mg/d)	0.01 (0.02, 0.04) 0.426	−0.01 (0.04, 0.02) 0.541	0 (−0.02, 0.03) 0.683	0 (−0.02, 0.03) 0.819	0.01 (−0.03, 0.05) 0.686	0.03 (−0.01, 0.07) 0.143	0.02 (−0.01, 0.05) 0.21	0.01 (−0.02, 0.04) 0.664	0.194
Child weekday physical activity score	−0.04 (−0.09, 0.01) 0.154	0 (−0.05, 0.05) 0.987	0.02 (−0.02, 0.07) 0.237	0 (−0.04, 0.04) 0.996	−0.03 (−0.1, 0.04) 0.38	−0.04 (−0.11, 0.03) 0.229	0 (−0.06, 0.05) 0.914	0.03 (−0.02, 0.09) 0.271	0.066

lengths) as measured by DXA at 3 years of age (Table 5). In our adjusted analysis, the only maternal variable significantly associated with child long bone length was maternal height (across all 8 bone lengths, $p = 0.0456$). No association was observed between any other maternal variables including nutrient intakes and offspring bone lengths at 3 years of age.

Our unadjusted multivariate linear regression analyses revealed the following factors were statistically significant: maternal height, infant birth weight, infant birth length, child weight z-score at 3 years, child calcium intake at 3 years, and child weekday physical activity score. After adding these variables to an adjusted multivariate linear regression model (Table 5), only three remained as statistically significant: maternal height, infant birth length, and child weight z score at 3 years.

In the secondary analysis (Fig. 1), only child weight z-score at 3 years remained significantly associated with each of other bone trait outcomes: child BMC z-score, child total body BMC, and child whole body minus the head BMC. The other factors found significant in the primary analysis were not associated with any of the other bone trait outcomes.

4. Discussion

In a healthy cohort of predominantly European descent, maternal height, child birth length and child weight z-score were all associated with child bone length traits measured with a novel method isolating limbs from DXA scans. Of particular note, we did not observe an association between maternal serum 25(OH)D concentrations in the third trimester of pregnancy and child long bone length at 3 years of age as previously observed in some [20] but not all [6,19] studies assessing infant bone length in utero and in childhood. In our secondary analysis, child weight z-score at 3 years was the only factor consistently and significantly associated with child whole body BMC, BMC z-score, and whole body minus the head BMC. These findings suggest that genetic traits have the most influence on child bone size and mineral content in early life. These observations align with reported evidence of fetal and maternal genetics accounting for 31% and 27%, respectively, of the normal variation in birth length while environmental factors have been reported to only account for 9% of the normal variation in birth length [35]. Similar results have been reported with birth weight, where 31% and 22% of normal variation was accounted by fetal and maternal genetic factors [35]. Paternal height has also been associated with infant's limb length at birth [36], supporting a strong influence of both maternal and paternal genetics over environmental factors on infant growth. Studies documenting the relationship between birth length and linear growth during early childhood, although sparse, have demonstrated a continued relationship between birth length and growth up to 16 years of age [37]. Similarly, birth weight has been reported to positively correlate with childhood linear growth throughout the entire spectrum of birth weights [38]. Taken together, these studies demonstrate the importance of parental genetic contributions over fetal, infant and childhood environmental influences during childhood growth, and support our findings of associations between maternal height, child birth length and child weight z-scores and long bone length at 3 years of age.

The influence of maternal vitamin D status during pregnancy on bone outcomes in the offspring has been the focus of several studies and reviews but the findings are inconsistent. Our observations that maternal vitamin D status is not associated with child bone length at 3 years are in line with results from a systematic review and meta-analysis of 12 observational studies that did not demonstrate a relationship between maternal vitamin D status and birth length [6]. For bone length beyond birth, a recent systematic review of randomized controlled trials found an association between maternal vitamin D supplementation and greater infant length at one year of age [39], but lack of measures of infant anthropometry led to only two out of the 35 identified trials to be analyzed for infant length. A meta-regression

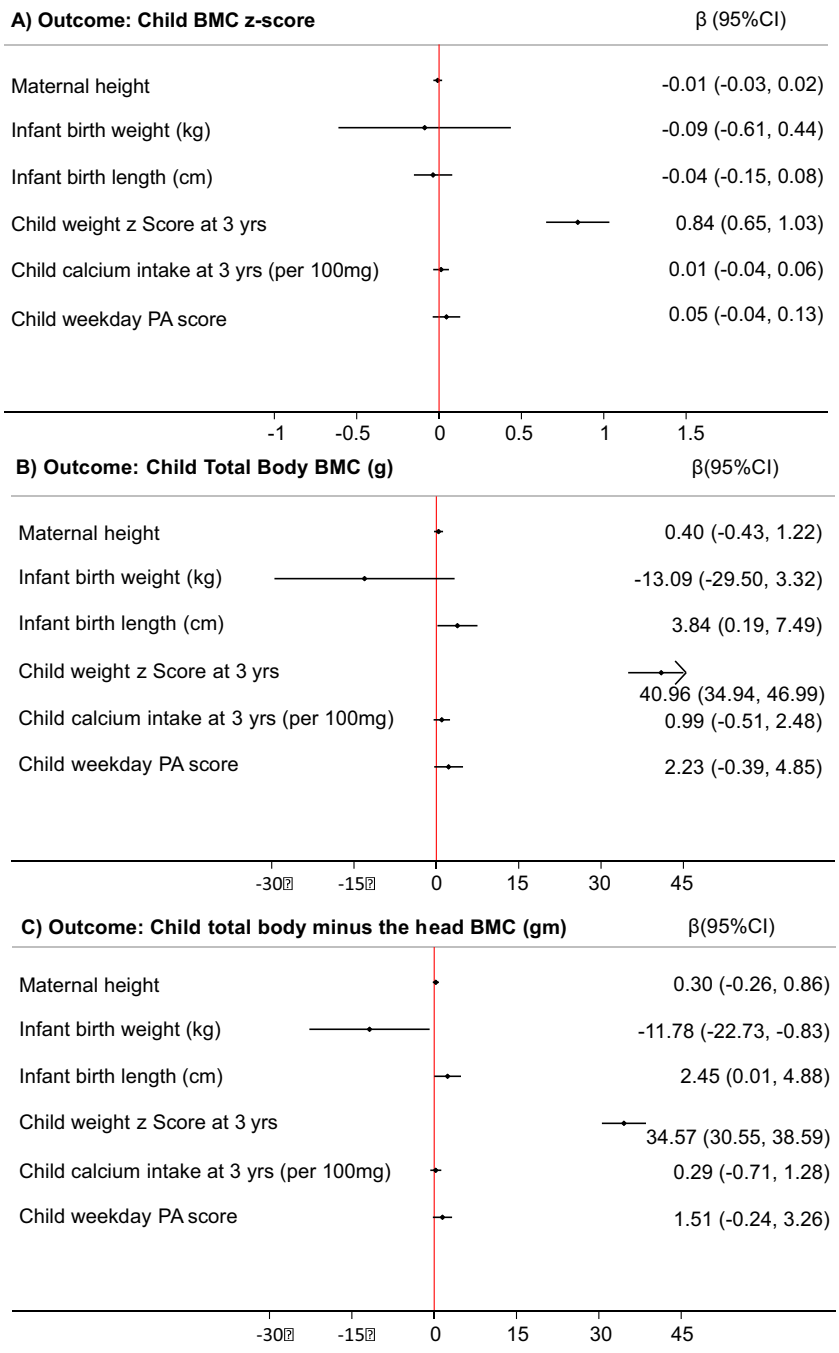

Fig. 1. Forest plots of the adjusted linear regression models for bone health outcomes: A) Child BMC z-score, B) child total body BMC, and C) child total body minus the head BMC. The models adjust for the significant factors identified from the primary multivariate analysis of 8 bone lengths.

could not be performed due to the low number of eligible interventions and omission of important covariates such as maternal body fat, maternal dietary intake, infant season of birth and duration of breastfeeding in the analysis. Only one other study to our knowledge measured leg bone length of children at 2 and 3 years of age, but a high lost to follow up of 61–79% limited the interpretation of their results [40].

Another possible explanation for the inconsistency in the association between maternal 25(OH)D concentrations and infant bone length is that in most previous studies' measures of bone length were estimated by measuring total body length or height using stadiometers, which is an important limitation. A direct measure of individual bone length such as the one employed in this study is likely a more accurate measure of limb length than body height [23]. To date, length of individual bones has only been measured from ultrasound scans to derive fetal bone length and its relationship to maternal variables during fetal gestation and at birth. Measurements such as crown-rump, femur and humerus lengths by ultrasound during the second and third trimester correlated with maternal 25(OH)D concentrations in early pregnancy in Korean, European descendants and African American populations [16,17,50,51]. To our knowledge, no one has ever reported on bone length derived from DXA scans in children. Our study thus extends the knowledge of prenatal programming of bone health of toddlers.

In studies that focused on maternal vitamin D status and bone mass, the findings are also inconsistent. Our results are consistent with those of Lawlor et al. [41] in British children who measured total body less head bone mineral content at 9.9 years in 3960 mother infant pairs and found no association with maternal serum 25(OH)D in pregnancy. Their statistical models were adjusted for maternal age, offspring sex, birth

weight, gestational age, and offspring height, lean mass, and fat mass, but not dietary or physical activity. A meta-analysis of 12 observational studies supported a positive relationship between maternal vitamin D status and offspring bone mass [6]. However, the contrast of such reports with our study may relate to lack of adjustment of the association between maternal-offspring factors and infant outcomes for a number of lifestyle factors, such as nutrition, physical activity, and season of birth in their analysis models. Inclusion of lifestyle factors as covariates in our statistical models was based on evidence that these factors can influence the relationship between maternal 25(OH)D concentrations and children outcomes [42].

Another example of the variation in factors influencing child bone length that exists across studies is the vitamin D status of pregnant women. In our study, the overall adequacy of maternal vitamin D status is reflective of a well-nourished population with low prevalence of vitamin D deficiency. This finding aligns with other observational studies with comparable study design in which no associations were observed between maternal vitamin D status and markers of prenatal and infant bone growth when mothers had adequate vitamin D status (e.g. mean or median serum maternal 25(OH)D concentration $\geqq$ 60 nmol/L) [13,14,43–45]. An adverse effect of an insufficient maternal vitamin D status on offspring bone growth was reported with maternal 25(OH)D $\leq$ 40 nmol/L, the suggested threshold below which programming effects would be observed in the children [46]. As most participants in this cohort were vitamin D sufficient, the lack of association with programming on bone health in the offspring is not surprising.

Maternal vitamin D status is known to vary with maternal ethnicity, sun exposure and vitamin D intake from food and supplements. Maternal serum 25(OH)D concentrations during pregnancy vary greatly by region and ethnicity [47], yet existing data are inconclusive as to how ethnicity may modulate the relationship with offspring bone metabolism. The majority of our cohort self-reported to be of European descent. Our results align with studies conducted in cohorts of European descent that also found no relationship between maternal vitamin D status and infant bone length [18,19,21,48,49]. However, in other studies a positive relationship was observed between maternal vitamin D status and infant height or bone length in groups of predominantly European descendants [15,46,50–53]. The impact of ethnicity on vitamin D metabolism might be more complex than what was originally reported, due to wide variation in skin colors, geographical region and clothing and living conditions [54]. For example, no association was observed in the few studies performed on Gambian, Iranian, Korean, Persian, Bengali and multi-ethnic populations [16,45,55–58], but a significant positive relationship was observed between maternal 25(OH)D concentrations and infant bone health early in life in Asian and African American populations [2,13,17,22,59–62].

Since many nutrients are important for bone health we investigated other aspects of maternal and child diet but found no significant associations with bone length. For calcium, which is critical to fetal bone development during the third trimester [63], the mothers consumed an average of 1997 mg of calcium per day, which is over twice the EAR, again suggesting a well-nourished population. The existence of a threshold type behaviour of calcium intake in relation to fetal long bone growth has been reported [17]. A significant difference was observed between fetal long bone z-scores of mothers with serum 25(OH)D < 50 nmol/L while simultaneously consuming < 1100 mg calcium/day as compared to mothers with 25(OH)D > 50 nmol/L [17]. The same relationship was not observed when calcium intake was > 1100 mg/day. Since the mothers in our study were consuming on average more than the suggested threshold of 1100 mg/day, it may be another possible explanation for the lack of an observed correlation between maternal 25(OH)D concentrations and children long bone length.

The use of a measure of childhood long bone length is novel in this study. Length board measurements rely on the child's height as a proxy for limb length; however, timing of both child growth and height measurements can significantly alter the expected ratio of limb length to height [64]. A direct measure of limb length by DXA scan, such as that which was performed in this study, or through more manual measurements such as a kneemometer [65] should provide greater confidence in making inferences about the relation between maternal 25(OH)D concentrations and limb length. We believe that our method of measuring individual limb length improves on the measurement limitations of birth length or children standing height [23], and allow for testing the associations between maternal and child characteristics with a quantitative measure of individual bone lengths.

Another strength of the study is both the sample size of over 300 and low loss to follow-up (< 10% at the 3 year visit). Other similar studies have lost over 20% of participants to follow-up [19,61]. Our primary outcome of bone length was obtained using the gold standard DXA for child anthropometric measurements, while the primary exposure variable was measured using the gold standard LC-MS/MS technique for serum 25(OH)D concentrations [66]. The novel software used to evaluate the limb length from the DXA scans pictures allowed ex-vivo measures of long bone length utilizing DXA scan images. Finally, our study targets measures that reflect intrauterine and early life factors that may impact on bone development – critical periods for programming of bone [67]. In contrast, most epidemiological evidence on the association between maternal 25(OH)D concentrations during pregnancy and childhood bone growth indicators have measured offspring at older ages (5 to 20 years) [14,15,19,42,43].

The limitations of our study were the homogenous nature of recruited mothers as the majority (87%) of mothers self-identified as being of European decent, limiting the external validity of our results. Another limitation is that the mothers were all well-nourished. Taken together the results from this study should not be extrapolated to infer possible associations between maternal serum 25(OH)D concentrations and child limb length in groups with either different demographics or less adequate nutrient intake. Another limitation inherent in this study is related to the MATLAB software which we used to compute bone lengths from DXA scans of our 3 year old children. DXA devices typically output x-rays beams that are well collimated in the axial direction (parallel), but fan beam collimated in the trans-axial direction. As a result, the parallel/fan beam nature of DXA implies that length can be accurately determined in the axial direction, but with less accuracy in the fan beam direction due to the beam divergence, with this error compounding with increasing height off the bed. In this work, the assumption was made that the measured bones were all at the same depth, equivalent to resting on the table. Phantom objects of known lengths were imaged over a 10 cm height range and less than a 2% deviation between actual length and measured lengths was observed. With this caveat, measurements should be treated with caution until further validation of this method is published.

5. Conclusion

In conclusion, in a healthy cohort of predominantly European descendants, maternal height, child birth length and child weight z-score were the factors associated with children's bone length traits as measured by DXA using a MATLAB software. This was an expected result due to the relative contribution of maternal and paternal genetic factors to neonatal and childhood growth. The lack of associations between maternal serum 25(OH)D concentrations in the third trimester of pregnancy and offspring bone lengths at 3 years of age may reflect that our cohort was a nutritionally healthy population with adequate serum 25(OH)D concentrations and adequate intakes of protein and calcium compared to other studies. It may also reflect differences in the measurement tool employed across studies to measure bone length. To our knowledge, there are no published studies that can be directly compared to our measures of 8 individual long bone lengths, which may offer greater accuracy of limb length. Future studies are necessary using similar software in combination with gold standard biochemical and anthropometric measurements to investigate relationships in

populations that are of either differential ethnic origin or less well-nourished. To target less well-nourished populations and evaluate possible threshold behaviour between 25(OH)D concentrations and childhood limb length a case-control study design selecting for 25(OH)D deficient (< 30 nmol/L) mothers could be used.

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CRediT authorship contribution statement

Andrew Beardsall: Data curation, Visualization, Writing - original draft, Writing - review & editing. **Maude Perreault**: Data curation, Visualization, Writing - original draft, Writing - review & editing. **Troy Farncombe**: Software, Writing - review & editing. **Thuva Vanniyasingam**: Data curation, Software, Validation, Visualization, Writing - review & editing. **Lehana Thabane**: Validation, Writing - review & editing. **Koon K. Teo**: Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Stephanie A. Atkinson**: Conceptualization, Funding acquisition, Project administration, Investigation, Writing - original draft, Writing - review & editing, Supervision.

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