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# The Influence of Maternal Factors on Offspring Bone Mass Accrual in Early Life

**Malek MW, Fields DA, Malek AJ, Hanks LJ and Casazza K***

*School of Medicine, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of Alabama at Birmingham, Birmingham, AL, USA*

*Section of Endocrinology and Diabetes, Department of Pediatrics and Children's Hospital Foundation Metabolic Research Program, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA*

***Corresponding Author:** Krista Casazza, School of Medicine, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of Alabama at Birmingham, Birmingham, AL, USA.

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## Abstract

**Background:** Infancy represents a critical period in which adequate skeletal development impacts long-term skeletal health. Maternal BMI and mode of feeding (i.e. breast feeding (BF) or formula feeding (FF)) are modifiable factors that contribute to infant bone development. The objective of this study is to evaluate bone mineral content (BMC) in the first 36 months of life and the contribution of maternal BMI and mode of feeding.

**Methods:** One-hundred and fifty-two mother-infant dyads were included. Infants' height, weight, length, and body composition were assessed at ages 6, 12, and 36 months. Pre-gravid maternal BMI, infant feeding mode during the first 6 months of life data was also collected. Differences in BMC between FF vs. BF infants as well as differences in BMC in infants from overweight vs. normal weight mothers were evaluated by t-tests and linear regression analysis.

**Results:** Seventy percent of infants were exclusively BF for at least one month and 66% of mothers were of normal BMI prior to pregnancy. BMC increased approximately 3.5-fold between ages 6- and 36-months. At 6- to 12-months, there was a significant increase in BMC in FF compared to BF infants ($p = 0.0001$). The differences in BMC between 12-and 36-months ($p = 0.25$) and 6- and 36-months ($p = 0.64$) were not significant. FF females increased BMC at 6-months ($p = 0.120$), with significantly greater BMC at 12- ($p = 0.044$), and 36-months ($p = 0.033$). In FF males BMC at 6-($p = 0.093$) and 12-months ($p = 0.172$) increased with no differences between groups observed at 36 months. There were significant differences in BMC between infants born with a maternal BMI≤ 25 compared to those > 25 were observed at 6-months in the total population ($p = 0.027$) and female ($p = 0.016$) infants. There was no association between maternal BMI and BMC in males at any age.

**Conclusions:** Increases in BMC are differentially affected by mode of feeding in the first six months with FF infants experiencing greater gains. The contribution of feeding mode to gains in BMC manifests to a greater extent on female infants compared to males. Further, maternal BMI is positively associated with female infant BMC but not male BMC.

***Keywords:*** *Infant Feeding; Body Mass Index; Bone Mineral Content; Linear Regression*

## Abbreviations

BMC: Bone Mineral Content; DXA: Dual Energy X-ray Absorptiometry: BF: Breastfed; FF: Formula Fed

## Introduction

Postnatal growth trajectories are highly dependent upon exposures in utero (e.g. maternal obesity) as well as in the postnatal period (e.g. breastfeeding) [1-3]. To date, most studies evaluate the effect of these exposures and the impact primarily focused on obesity and related outcomes [3-7]. While maternal body mass index (BMI) and mode of feeding (i.e. breast (BF) vs. formula (FF)) has been well-described as a significant contributor to birth weight and offspring size [8,9] less attention has been given to the contribution of these factors on bone mass accrual during this critical period in linear growth [10]. Due to the trajectory of the skeletal growth as well as the strength structural properties of the skeleton are profoundly influenced by growth during the first year of life11, assessment of modifiable determinants of bone mass development in infancy is needed to guide recommendations for early life exposures [1,12-16] which may affect long-term bone health.

Mode of feeding and maternal BMI are potential modifiable exposures [1,2,12,13,17]. Although the World Health Organization (WHO) considers exclusively breastfed for the first six months of life to be the gold standard for ideal body composition in infants [18], this recommendation is largely based on observational studies evaluating obesity risk [5,19] and effects on bone growth and development has not been adequately explored. Breast milk has a significantly different micronutrient profile than formula [17,20]. Therefore, the micronutrient profile may influence bone mass accrual differently than breast milk through provision of diverse concentrations of nutrients to the growing newborn [10,17,21]. Despite a lower concentration of calcium and phosphorus in human milk, the bioavailability and absorption of these nutrients is greater formula with studies indicating BF infants have on average 200 mg of calcium per day greater intake [2,22-25]. Further, the potentiating effect of breast milk on bone development may stem from a non-nutritional factors which may lead to changes in the programming of bone cells [26]. However, it is unclear whether altered growth (presumptively greater) is beneficial to bone development, beyond increases in overall size [27-29]. Pre-gravid maternal BMI, which is directly related to offspring size [5,8,30]. Maternal size and nutritional status in pregnancy contribute to infant bone mineral mass [2,31,32]. For example, maternal obesity and gestational diabetes, often co-occurring, is associated with macrosomia [8,9,30], which has been correlated with greater infant length [1,12] but also poor bone and metabolic health. In one study, infant birth weight was positively associated to femoral neck cross sectional area in a cohort of elderly men [33]. Therefore, further investigation of the relationship between pre-gravid BMI and infant bone mass accrual in early development is important to optimize adult skeletal potential.

Studies evaluating the impact of BF on bone mass accretion have focused on the comparison of different infant formulae, rather than breast-feeding characteristics (i.e. exclusivity and duration). Other studies retrospectively evaluating the effect of breast-feeding on adolescent bone mass have reported equivocal results [34]. The objective of this study was to determine the differences in bone mass development, i.e. bone mineral content (BMC) between the following groups at 6, 12, and 36 months of age: 1) infants formula fed (FF) versus those exclusively breast fed (BF) for a minimum of one month 2) infants born to overweight/obese mothers with a pre-pregnancy BMI > 25 kg/m$^2$ versus normal weight mothers.

The hypothesis was two-fold: 1) infants who were formula fed would have higher BMC than BF infants at 6, 12, and 36 months of age; 2) infants born to mothers with a pre-pregnancy BMI > 25 kg/m$^2$ would have greater BMC than infants born to mothers with a pre-pregnancy BMI ≤ 25 kg/m$^2$.

## Methods

### Study Overview

One hundred and fifty-two mother/infant dyads were tracked at ages 6 months, 12 months, and 36 months. The overall study design and preliminary results were described in a previous study that examined the relationships between breast milk hormones and inflammatory markers [35]. The data reported here describe relationships between infant body composition and breast milk sugar content that were not explored in the previous work. To be included in the study, mothers met the following inclusion criteria: a) 21 to 45 years of age at the time of delivery, b) pre-gravid BMI between 18.5 to 40 kg/m$^2$, c) healthy pregnancy defined as < 3 days in hospital following delivery. Infant inclusion was a) singleton birth, b) term pregnancy (gestational age > 37 but <42 weeks) and c) birth weight > 2,500 grams but < 4,500 grams. Mothers were excluded for: a) alcohol consumption > 1 drink per week during pregnancy/lactation, b) tobacco consumption during pregnancy/lactation, c) inability to speak/understand English, and infants were excluded if they had known congenital metabolic, endocrine disease, or congenital illness affecting infant feeding or growth.

Almost two-thirds of the mothers were of normal weight defined as a pre-pregnancy BMI < 18.5 < 25.0 kg/m$^2$ (n = 94); with the remaining participants classified as overweight/obese (≥ 25.0 kg/m$^2$; n = 58). Maternal related variables (socioeconomic status, pregravid BMI) were obtained from medical records where possible.

Some data were obtained directly from the patient when available. Parental consent was obtained prior to all testing procedures. All testing took place at the University of Oklahoma Health Sciences Center. The Institutional Review Board at the University of Oklahoma approved all procedures for human participation.

### Anthropometrics and Body Composition

Recumbent length was measured in duplicate using a Seca 416 infantometer (Seca, Hamburg, Germany) with both measures being within 0.1 cm. Nude body weight was measured in duplicate with a Seca 728 scale (Seca, Hamburg, Germany) with both measures being within 10 g. On the rare occasion, these measures exceeded the criteria set forth, a third measure was obtained and the two closest values averaged. Total adiposity (% fat), fat mass (g), lean mass (g), and bone mineral content (g) were collected using a Lunar iDXA (General Electric, Fairfield, CT, USA) scanner as described previously [36]. During the scan, the infant wore only a diaper and was swaddled in a light blanket. The principal investigator (DAF) positioned all infants and performed subsequent scan analyses. To improve compliance and minimize movement, the infant was tested in a darkened room while a DVD played a movie.

### Mode of Feeding

The 'breastfed' cohort was defined as infants exclusively breastfed for a minimum of 1 month (n = 106). The remaining participants were exclusively formula fed starting at birth (n = 46). The infant underwent a whole-body dual energy X-ray absorptiometry (DXA) scan at each visit. Total body composition and (fat and fat-free mass) and bone mineral content (BMC) were collected using a Lunar iDXA (GE, Fairfield, CT) scanner described previously [7,35,37] while the infant was swaddled wearing only a diaper.

### Statistical Analysis

Data was analyzed using (SAS 9.3). Paired two-tailed t-tests were used to evaluate growth differences between BF and FF infants. Mean squared measures of BMC at 6, 12, and 36 months were generated comparing infants by mode of feeding (FF v. BF). The associations between BMC at 6, 12, and 36 months were studied using linear regression with infant BMC as the dependent variable, controlling for sex, birth weight (only in models evaluating growth at 6 months), race, and mother's pre-pregnancy BMI. Infant percent body fat was removed after initial analysis because it did not contribute to the relationship between BMC and mode of feeding ($p > 0.2$). To determine sexual dimorphism in growth, sex-stratified models were used. The same statistical analysis was performed comparing infants by mothers pre-pregnancy BMI (≤ 25 v. > 25). The linear regression model used maternal BMI as the dependent variable, controlling for sex, birth weight (only at 6 months), infant length, mode of feeding, and race.

## Results

Approximately 79% of the dyads were self-reported to be white (Table 1). Infants were carried to term (~39 weeks) on average weighing 3500g (7.7 lbs), were 51 cm (20.1 in) long with approximately half of the infants were female. Maternal age was ~28 years with a pre-gravid BMI of 26kg/m$^2$ and on average gravid weight gain was 14 kg (31lbs). Approximately 70% of the infants were exclusively BF for at least one month in the total population. Almost two-thirds of the mothers were of normal weight defined as a pre-pregnancy BMI < 25.0 kg/m$^2$ (n = 94). 25.6% of normal weight mothers reported exclusive breastfeeding, while 37.1% of overweight (BMI > 25.0; n = 58) indicated exclusive breastfeeding for at least one month.

BMC increased approximately 3.5-fold between ages 6- and 36-months. Figure 1 illustrates the magnitude of increases in BMC from 6- to 12-months (0.140 to 0.206), 12- to 36-months (0.206 to 0.483), and 6- to 36-months (0.140 to 0.483). There were greater increases in BMC between 12- and 36-months in the total population (0.276 g/cm), males (0.29 g/cm), and females (0.266 g/cm) than there were between 6- and 12-months in the same populations, respectively (0.067 g/cm; 0.058 g/cm; 0.075 g/cm). Female infants had greater increase in BMC between 6- and 12 months (0.075 g/cm) than males (0.058 g/cm). However, male infants made marginally greater increases in BMC between 12- and 36-months (0.29 g/cm) and 6- to 36-months (0.348 g/cm), than did females at the same respective ages (0.266 g/cm; 0.341 g/cm).

| Infants (n = 152) | % |
|---|---|
| Race | |
| White | 78.95 |
| Black | 6.58 |
| Other | 14.47 |
| Gender | |
| Girls | 50.65 |
| Boys | 49.34 |
| Mode of feeding | |
| BF | 69.74 |
| FF | 30.26 |
| | **Mean + SD** |
| Birth weight, kg | 3.47 ± 0.4 |
| Birth length, cm | 50.98 ± 2.4 |
| Gestational age, weeks | 39.31 ± 1.1 |
| **Mothers** | **%** |
| Income, | |
| <$30,000 | 16.45 |
| $30,000-$60,000 | 29.61 |
| >$60,000-$90,000 | 30.26 |
| >$90,000 | 14.47 |
| Income Data Not Reported | 9.21 |
| | **Mean + SD** |
| Age at delivery, years | 27.8 ± 4.4 |
| Parity, # live births | 2.1 ± 1.1 |
| Height, cm | 165.3 ± 7.16 |
| Weight gain in pregnancy, kg | 14.1 ± 6.2 |
| Pre-pregnancy Weight, kg | 71.05 ± 18.9 |
| Pre-pregnancy BMI | 25.89 ± 6.4 |

***Table 1:*** *Infant and Maternal Characteristics Mean + Standard deviation (SD)*

*BF: Breastfed; FF: Formula Fed; BMI: Body Mass Index*

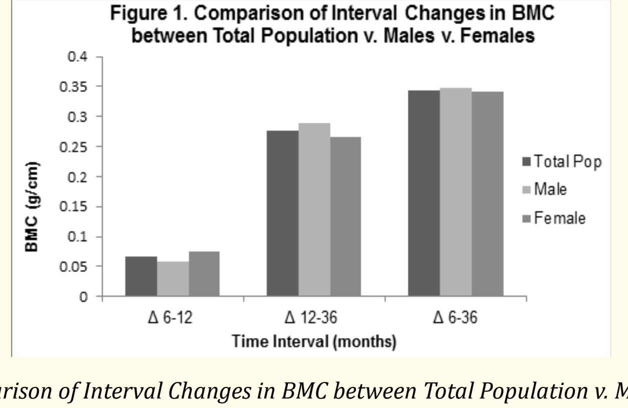


***Figure 1:*** *Comparison of Interval Changes in BMC between Total Population v. Males v. Females.*

*Bone mineral content assessed by dual-energy x-ray absorptiometry (BMC). Change in BMC from month six to one year of age (Δ6 - 12); Change in BMC from one year to three years of age (Δ12 - 36); Change in BMC from six months to three years of age (Δ6 - 36).*

Figure 2 illustrates the magnitude of increase of BMC between FF and BF infants from 6- to 12-months (0.147 to 0.226; 0.137 to 0.192), 12- to 36-months (0.226 to 0.485; 0.192 to 0.482), and 6- to 36-months (0.147 to 0.485; 0.137 to 0.482). At 6- to 12-months, there was a significant increase in BMC in FF (0.079 g/cm) compared to BF (0.06g/cm) infants ($p < 0.001$). However, BF infants' bone mass accrual between 12- and 36-months (0.29 g/cm) and 6- to 36-months (0.35 g/cm) surpassed FF infants during the same intervals, respectively (0.26 g/cm; 0.338 g/cm). The differences between BMC between 12-and 36-months ($p = 0.25$) and 6- and 36-months ($p = 0.64$) were not significant.

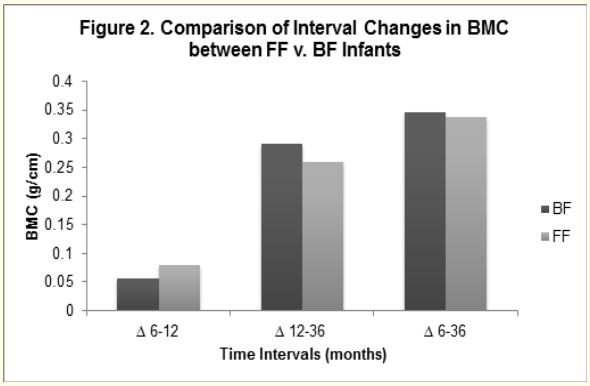


***Figure 2:*** *Comparison of Interval Changes in BMC between FF v. BF Infants.*

*Bone mineral content assessed by dual-energy x-ray absorptiometry (BMC). Change in BMC from month six to one year of age (Δ6 - 12); Change in BMC from one year to three years of age (Δ12 - 36); Change in BMC from six months to three years of age (Δ6 - 36).*

There were significant differences in BMC between FF and BF infants at 6- ($p = 0.037$) and 12-months ($p = 0.008$) in the overall sample after adjusting for birth weight at 6-months, length, sex, and race such that BMC was greater in formula fed infants (Table 2). The observed difference was independent of maternal BMI as inclusion of this variable maintained the higher BMC in formula fed infants at 6- ($p = 0.023$) and 12-months ($p = 0.016$). At 36 months, there were no observed differences in BMC between groups in either model. A sexual dimorphism was apparent such that when stratified by sex, the relationship appeared to be sexually dimorphic. FF females increased BMC at 6-months albeit not significantly ($p = 0.120$), with significantly greater BMC at 12- ($p = 0.044$), and 36-months ($p = 0.033$). In FF females, a non-significant increase in BMC at 6- ($p = 0.064$), 12- ($p = 0.064$), and 36- months ($p = 0.105$) was observed after maternal BMI was included as a covariate. In FF males BMC at 6-($p = 0.093$) and 12-months ($p = 0.172$) increased, albeit non-significantly, with no differences between groups observed at 36 months. The difference was attenuated after inclusion of maternal pre-gravid BMI to the sex-specific model for yielded similar result in males at 6 months ($p = 0.086$), without any difference in BMC at 12- or 36 months.

| BMC | | | |
|---|---|---|---|
| Age (months) | *Total | †Boys | Girls |
| 6 | p = 0.03 | p = 0.48 | p = 0.016 |
| 12 | p = 0.22 | p = 0.58 | p = 0.43 |
| 36 | p = 0.21 | p = 0.91 | p = 0.18 |
| Age (months) | **Total | ††Boys | Girls |
| 6 | p = 0.03 | p = 0.40 | p = 0.02 |
| 12 | p = 0.33 | p = 0.65 | p = 0.52 |
| 36 | p = 0.21 | p = 0.91 | p = 0.17 |

***Table 2:*** *Difference in BMC of infants with pregravid maternal BMI ≤ 25 v. > 25.*

*Age = age at assessment; BMC = bone mineral content*

**Adjusted for birth weight (at 6mo), sex, mode of feeding, length*

***Adjusted for birth weight (at 6mo), sex, mode of feeding, length, race*

*†Adjusted for birth weight (at 6mo), mode of feeding, length*

*††Adjusted for birth weight (at 6mo), mode of feeding, length, race*

Significant differences in BMC between infants born with a maternal BMI≤ 25 compared to those > 25 were observed at 6-months in the total population (p = 0.027) and female (p = 0.016) infants (Table 3).

| | Weight (kg) | | Length (cm) | | Percent Fat (%) | |
|---|---|---|---|---|---|---|
| Age (months) | FF | BF | FF | BF | FF | BF |
| 6 | 7.52 | 7.35 | 66.17 | 65.45 | 30.08 | 32.21 |
| | p = 0.40 | | p = 0.10 | | p = **0.003 | |
| 12 | 9.84 | 9.40 | 75.28 | 74.3 | 28.81 | 28.77 |
| | p = 0.09 | | p = 0.13 | | p = 0.96 | |
| 36 | 14.49 | 14.38 | 95.23 | 95.35 | 26.56 | 26.79 |
| | p = 0.74 | | p = 0.88 | | p = 0.79 | |

***Table 3:*** *Comparison in weight, length and percent body fat among breastfed (BF) vs formula fed (FF) children at 6, 12 and 36 months.*

***Significant = p-value ≤ 0.05*

*No difference in weight or length, but difference in percent fat demonstrated only at six months in formula-fed (FF) vs breastfed (BF) infants.*

There was no association between maternal BMI and BMC in males at any age. Including race to the model showed similar differences in BMC at 6-months in the total population (p = 0.026) and female (p = 0.017) infants.

BF infants had significantly greater percent fat than FF infants (p = 0.0031) at 6 months and had greater, though not significant, percent fat at 36 months (p = 0.7941) (Table 4). In males, there were no significant differences in length or weight. Percent fat also did not significantly differ between BF and FF males.

| Males | | | | | | |
|---|---|---|---|---|---|---|
| | Weight (kg) | | Length (cm) | | Percent Fat (%) | |
| Age (months) | FF | BF | FF | BF | FF | BF |
| 6 | 7.94 | 7.65 | 67.54 | 66.43 | 7.93 | 7.65 |
| | p = 0.28 | | p = 0.08 | | p = 0.28 | |
| 12 | 10.13 | 9.82 | 76.33 | 75.37 | 28.15 | 27.86 |
| | p = 0.32 | | p = 0.34 | | p = 0.84 | |
| 36 | 15.00 | 14.71 | 96.95 | 95.87 | 24.76 | 25.72 |
| | p = 0.48 | | p = 0.38 | | p = 0.45 | |
| **Females** | | | | | | |
| | Weight (kg) | | Length (cm) | | Percent Fat (%) | |
| | FF | BF | FF | BF | FF | BF |
| 6 | 7.15 | 7.04 | 64.94 | 64.39 | 30.27 | 32.86 |
| | p = 0.68 | | p = 0.38 | | p = 0.01 | |
| 12 | 9.63 | 8.96 | 74.55 | 73.20 | 29.14 | 29.67 |
| | p = 0.04 | | p = 0.09 | | p = 0.60 | |
| 36 | 14.19 | 13.97 | 94.23 | 94.73 | 27.36 | 27.95 |
| | p = 0.62 | | p = 0.63 | | p = 0.62 | |

***Table 4:*** *Average weight, length, and percent body fat across three years in formula-fed (FF) versus breastfed (BF) male and female infants.*

In females, FF infants were heavier than their BF counterparts at 12-months (p = 0.043). BF females had significantly greater percent fat at 6-mo than FF females (p = 0.0129).

## Discussion

Long-term bone health is influenced by a complex interaction of genetic, demographic, socioeconomic, hormonal and environmental factors beginning early in the life course. A recent review of modifiable risk factors for childhood obesity identified strong evidence for high maternal pregravid BMI and mode of feeding in offspring obesity [4,5]. Although the first three years of life represent an important period for bone development, few investigations have evaluated the contribution to modifiable factors on offspring bone growth. Understanding the contribution of modifiable factors in bone mass development is important to ensure adequate nutrition and supplementation supports optimum adult skeletal health. This study illustrated that there are significant gains in bone mass accrual after the first 12-months of life than there are in the first 6- months in the total population. In addition, female infants displayed greater increases in BMC than their male counterparts in the first 6-months of life. However, from 12- to 36 months, BMC in males' surpassed that in females'. These differences in growth velocity may represent the initiation of sexual dimorphism in bone health prior to overt differences in bone density observed in puberty [5]. The extent to which modifiable risk factors differentially affect strength-structural properties of body composition beyond the oft-described impact on adiposity warrants investigation.

The relative increases in BMC in the first 36 months of life, are greater than at any other point in life [19,38]. Exposures that may adversely affect bone accretion during this period impact long-term bone health. We observed greater BMC in FF infants compared to BF infants between 6- and 12-months, yet no difference in these groups between 12- and 36 months or 6- and 36 months. These findings suggest that source of nutriture differentially contributes to BMC quantity at distinct stages early in life.

Given benefits to nutritional status, cognitive and physical development, reducing mortality for the infant, and the rates of some chronic conditions in adult life, breastfeeding is universally recognized as the ideal way of feeding infants. Many studies also espouse a purported benefit of BF relative to FF on offspring obesity risk [5,19]; however, few have investigated a differential effect on bone in early years. Among six studies identified assessing the association of interest in childhood, three did not find association [9,10,14]; two found higher bone mass values among BF children [3,17], and one showed that BF children had lower BMC compared with those FF.

In the sex-stratified model FF females had significantly greater BMC at 12-, and 36-months when compared to FF males and the contribution was independent of maternal BMI. In a study evaluating adults, men who were BF for greater duration had lower BMC than those BF shorter time, with no effect of BF duration on BMC observed in women [39]. Mechanistic evaluation of nutrient delivery and utilization and a potential differential influence of offspring sex and body composition may provide further insight into guided interventions to optimize bone health during growth and development.

Despite lower concentration of calcium and phosphorus in human milk, the bioavailability and absorption of these nutrients is greater than formula (or cow's milk). Formula fed infants have a higher growth velocity than breastfed infants. It has been suggested that the main reason is the higher content of protein in formula which increases the secretion of growth promoting factors. Specifically, the content of specific free amino acids (FAA; e.g. glutamic acid, glutamate, the most abundant in human great milk), which influences appetite and growth. There are receptors for FAA in the oral cavity and gastrointestinal tract which speculatively serve as a satiety signal during feeding. The possible appetite regulating effect of FAA in the breastfed infant could play a role in the lower energy intake and slower growth in BF relative to FF fed infants, particularly during the first months of life. The content of glutamic acid is the highest from early lactation until after 2 months, whereas glutamine concentration is very low in colostrum and increases after 2 months. There is a large variation between mothers which may also be influenced by maternal BMI [40,41]. Conversely, potentiating effect of breast milk on bone development may stem from a non-nutritive factors [26].

An independent association on bone mass have been suggested as consequence of mother-fetus overnutrition, with disagreement regarding to long-term influence on long-term offspring bone health. Maternal BMI has been identified as a strong determinant of birth weight, offspring size; and, therefore, bone mass density of offspring [1,8,9,12]. Among infants with maternal BMI > 25, greater BMC at 6-months compared to those with maternal BMI ≤ 25. However, no differences in BMC at 12- or 36-months were observed and the effect was independent of race. When stratified by sex, there were no group differences in BMC. Females of mothers with a pregravid BMI >25 had significantly higher BMC at 6-months relative to female offspring of normal weight mothers, but there were no significant differences at 12- and 36-months. The study by Butte., *et al.* [42] concluded that the association between feeding mode and sex differences body composition, focused on fat mass and percent fat mass, in early infancy do not persist into the second year of life. Taken together, findings suggest that plasticity of bone development may be most affected in the first 6 months of life, with a potentially stronger influence in female offspring.

The WHO and American Academy of Pediatrics (AAP) recommend exclusive breastfeeding for optimal growth and development. It is unclear is "breast is truly best" when considering maternal metabolic control. It has been reported that BF versus FF infants have a "more desirable" growth up to two years of age [43-45]. However, maternal obesity pre-programming has also been reported such that obese mothers appear to be more likely to give birth to infants of greater birth weight and longitudinal studies are surfacing indicating a potential adverse effect of bone health [30,31]. Our population included mothers that breastfed longer than one month. However, accurate assessment of breastfeeding duration was not documented. Inconsistent results have been reported with BF duration and BMC over the life course [46]. Rapid growth and later development of metabolic anomalies have also been reported [47,48]. The relationship between nutrient availability, growth velocity and bone development, particularly BF among mothers with loss of metabolic control (e.g. gestational diabetes) warrants further investigation.

The strength of the study was the large variation in BMC and in weight, length and BMI making it possible to investigate the associations over a wide range. Limitations of the present study include the small sample size in this proof-of-concept study, limited length of follow-up (six months of age), and a lack of maternal and/or complementary dietary intake data that could help explain the relationship between BMC and maternal factors. Although women were instructed to exclusively breastfeed, it is possible that food introduction may have occurred in some infants during the study period and contributed to growth and body composition, particularly if infants were given access to milk/formula food products. Indeed, a recent study which evaluated the energy content of commercial infant and toddler food products found that foods aimed at complementary feeding in infants contain at a relatively greater sugar content than breast milk or formula, associated with more rapid growth, may confound results. It is highly likely that infants are exposed to complementary foods within the first few months of life (e.g., during breastfeeding and/or weaning when complementary foods are introduced to the diet), effect body composition development. Another potential limitation is that we have limited metabolic variables in the mothers. Furthermore, we used growth from birth to four months as a surrogate for average milk intake during this period. Other factors which might influence growth are the non-nutritive bioactive components of human milk, which were not measured. High levels of appetite regulating hormones in breast milk have been associated with high weight gain in early infancy. Thus, the appetite regulation may be different in FF infants regarding the effect of ingested appetite regulatory hormones as the presence of these hormones in formula is uncertain. Studies to support the findings and elucidate possible mechanisms are therefore warranted.

## Conclusions

Given the reciprocal relationship between fat and bone and its integral intersection during early body composition trajectories [49-51], we hypothesized that maternal factors reported to influence infant body fat would be influential in bone mass accrual in early life. Overall, this study suggests maternal factors influence mechanism by which infants accrue BMC. This work also opens the door for interventions aimed towards investigation of effects of BF and maternal BMI beyond the oft described, yet controversial protective effect of BF on obesity. This work also may provide guidance for interventions aimed towards recommendations for maternal lifestyle and potential to meaningfully impact the development of optimal bone phenotypes in later childhood and to investigative the mechanism. Future work should be performed with larger samples with longer follow-up (> 6 months) in order to establish whether the relationships observed between maternal exposure and infant growth meaningfully impact the development of body composition phenotypes in later childhood and to investigative the potential bone metabolic pathways affected. In conclusion, we provide preliminary evidence that maternal factors impact infant growth, to a greater extent in female infants, impacting growth and body composition during the first three years of life.

## Financial Disclosure

DAF received funding for this study from Nestle; MWM, KC, LJH, and AJM have nothing to disclose.

## Clinical Trials Name and Registry Number

N/A.

## Contributors Statement

Casazza, K: conceived project, provided statistical analysis, and critically reviewed the paper. Fields, DA: collected data, drafted methods section, and critically reviewed the paper. Hanks, LJ: provided scientific consultation and critical review of the paper. Malek, AJ: analyzed data and revised paper. Malek, MW: conceived project, analyzed data, drafted and critically reviewed the paper.

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