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Growth from birth to adolescence and bone mineral density in young adults: The 1993 Pelotas birth cohort

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ABSTRACT

Background: The study examined the association of body size (weight and length) at birth and gain in height and weight during childhood and adolescence with areal bone mineral density (aBMD) in adulthood for women and men.

Methods: 756 members (335 men and 421 women) of the 1993 Pelotas (Brazil) Birth cohort were studied. Data on weight and length/height were obtained at birth and subsequent follow-ups at 1, 4, 11, 15, 18, and 22 years of age and specific z scores were calculated by sex. The outcome was whole body aBMD (g/cm^2) measured at 22 years of age using dual-energy X-ray absorptiometry (DXA). The effects of exposures, weight and length/height gain, were analyzed using conditional relative weight (CWh) and conditional length/height (CH). Linear regression models were adjusted for multiple confounders, including mother's educational level, family income, maternal smoking during pregnancy, gestational age, breastfeeding and skin color.

Results: In the adjusted models, among men greater height gain at 4, 11, and 18 years of age was associated with higher whole body aBMD, and the result with greatest magnitude was at 11 years of age (β 0.018 g/cm^2; 95%CI 0.006; 0.030). Among women, aBMD was associated with height gain at all assessments from 1–15 years, with greatest effect size at 4 years of age (β 0.017 g/cm^2; 95%CI 0.007; 0.027). Regarding to body weight, among men, greater weight at 4 and 15 years were associated with higher aBMD, with the highest coefficients for 15 years of age (β 0.015 g/cm^2; 95%CI 0.003; 0.027); for women, except at birth, all weight gain variables were associated with aBMD and the highest coefficients were observed at 4 years (β 0.025 g/cm^2; 95%CI 0.015; 0.035).

Conclusions: In this birth cohort, height and weight gain, especially from 4 to 15 years have important positive implications for aBMD to early adulthood.

1. Introduction

Bone mineral density (BMD) is used as a tool for the diagnosis of osteoporosis [1–4]. Each standard deviation of reduction in BMD is associated with a two to threefold increase in the risk of fracture among adults and the elderly [5,6]. Throughout life, bone mass quantity and quality are determined by an array of genetic and environmental factors and are also dependent on prior experiences such as nutritional status, calorie intake, physical activity, and hormone levels [1]. As such, it has been proposed that the determinant factors of bone mineral mass in advanced age are to be found in the initial stages of development in early life [7].

The anthropometric phenotype comprises a set of partially modifiable influences on bone strength [2]. The foundation of bone strength is

Abbreviation: aBMD, areal bone mineral density; BMD, Bone mineral density; BMC, Bone mineral content; BMI, Body mass index; CH, Conditional length/height; CWh, Conditional relative weight; DXA, dual-energy X-ray absorptiometry; REDCap, Research Electronic Data Capture

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laid in utero, and subsequent growth in infancy, childhood, and adolescence is essential for the acquisition of adult peak bone mass [8]. The increased overall exposure to weight during growth, in dose and/or duration, may positively influence bone health as a consequence of greater and/or longer exposure to loading, especially from the lean component [9]. Many studies have consistently demonstrated a positive correlation between birth weight and bone mass [8,10–15], supporting the intrauterine programming hypothesis. Prospective studies examining the high rate of height and weight growth trajectory in relation to bone mass in adults and the elderly have identified postnatal growth as an important determinant, particularly as predictive of future bone phenotype [7,16,17] and risk of fracture [18,19].

The term growth is employed to refer to changes over time in any of the body's measurements [20]. Assessment of human growth requires observations in series [20], collecting longitudinal data with the objective of estimating periods of development with sensitivity for a given outcome [21]. For example, investigations that enable study of possible relationships between growth and bone health at later ages are useful for evaluating whether preventative measures implemented at certain ages could improve bone health in the elderly [7].

Recent investigations have discussed the fact that body size (height and weight) at the time of bone measurement is recognized as having a great deal of influence on bone mineral mass [7,16,17]. Results demonstrate that the associations between growth and bone mass are attenuated when analyses are adjusted for these variables, indicating that the majority of influence possibly resides in skeleton envelope size [7,17].

The majority of studies investigating childhood growth and bone health or risk of fractures in adults have concentrated on associations between birth weight or weight at 1 year of age and bone phenotype [17]. To date, few studies have examined the entire growth trajectory in relation to bone mass in adults, including prepubescent, pubescent, and postpubescent periods [7,16,17]. However, those studies assessed outcomes in populations that were older than this cohort [16] or even elderly [7,17] and some analyses were not stratified by sex [16]. Since this study identified associations already present at 22 years of age, studying these relationships at earlier ages could help delay or avoid exacerbation of bone loss.

Therefore, considering both prior and contemporary factors that influence people's BMD, we examine the effects of body size at birth and growth in length/height and weight at different points during childhood and adolescence on the BMD in early adulthood of members of a birth cohort.

2. Methods

2.1. Pelotas birth cohort

In 1993, all maternity units located in the city of Pelotas, RS, Brazil, were visited daily and 5265 births to women living in the urban zone of Pelotas were recorded from January 1 to December 31 [22]. A total of 5249 mothers agreed to take part in the study and their newborn infants were examined. The members of this cohort were followed up at several different times. More details on the methodology employed have been published elsewhere [22].

This study analyzes data from seven follow-ups: perinatal and at the ages of 1, 4, 11, 15, 18, and 22 years. Follow-ups at 1 year and 4 years of age were conducted with a subsample of the original cohort. For both of these follow-ups, the same children comprised the target population (n = 1460), which were a subset made up of all children born with low birth weight (n = 510) and a random sample of 20% of the children who had not been born with low birth weight (n = 950). More details on follow-ups have been described elsewhere. [22–24] Home visits were conducted at each follow-up except for those at 18 and 22 years of age, when the subjects attended the university's research clinic, where they were interviewed to complete digital questionnaires, underwent physical examinations, and had biological samples taken [23,24]. The last follow-up employed a questionnaire tested in advance that was constructed using the REDCap system (Research Electronic Data Capture) [25] for electronic data collection followed by construction of a database.

All of the follow-ups of the 1993 Pelotas Birth Cohort were approved by the Ethics Committee in Research of the School of Medicine of the Universidade Federal de Pelotas. The most recent protocol approved is number 1.250.366. At all stages of follow-up, participants (or their legal guardians) signed free and informed consent forms. Verbal consent was given for the perinatal phase.

2.2. Assessment of the outcome

Whole body areal bone mineral density (aBMD) (g/cm^2) was measured using a dual-energy X-ray absorptiometry (DXA) scanner (Lunar Prodigy Advance – GE®), calibrated daily. In accordance with the manufacturer's recommendations, pregnant women or those with a suspicion of pregnancy, people in wheelchairs, with bone and joint deformities, weight exceeding 120 kg, or height greater than 192 cm were not examined. During the examinations and for standardization, participants were given appropriate clothing and did not wear anything made from metal.

2.3. Assessment of exposures

Birth weight and length were recorded at the maternity units at birth. At follow-up visits, measurements were taken at participants' homes and at the 18 and 22-year follow-ups measurements were taken at the research clinic. On every occasion, weight and length or height were measured by professionals who had been trained according to Lohman's [26] techniques and standardized as proposed by Habicht [27].

Growth patterns were studied at several points of life: infancy (from birth to 1 year of age), early and mid-childhood (1–4 and 4–11 years of age, respectively) and early and late adolescence (11–15 and 15–18 years of age, respectively). For each age interval, the effects of weight gain and linear growth were analyzed using conditional relative weight (CWh) and conditional length/height (CH) as proposed by Adair et al. [28]. CWh considers current height and previous weights, lengths, or heights and CH considers previous weight and length or height measurements, but not current weight [28].

To enable calculation of conditional measures, first, specific z scores were calculated by sex for each weight and length from prior follow-ups. The z score measures (weight or height) for a given age were regressed on the z-scores of all previous measurements using linear regressions. The conditional measure is represented by the standardized residuals of the regression and indicates the extent to which a participant's measurements deviate from the expected, on the basis of prior growth and the cohort's mean growth. It can be interpreted as a measure of how much more quickly or more slowly weight or length/height change over the course of a period of time. For example, an adolescent with a positive CWh value from 4 to 11 years of age gained more weight relative to his or her own previous weights and lengths/heights in relation to all the other members of the cohort. Since the conditional variables are not correlated, they can be included in a multiple regression model without violating any assumptions of collinearity [29].

2.4. Covariates

The following were analyzed: sex (male, female), mother's educational level (0–4, 5–8, 9–11, ≥12 years of study), family income (≤1; 1.1–3; 3.1–6; > 6 times the minimum wage), maternal smoking during pregnancy (yes; no), gestational age (< 34, 34–36, 37–40, > 40 weeks) total breastfeeding duration (months), and self-report skin color collected at 15 years of age (white; black; brown; or other).

2.5. Statistical analysis

All statistical analyses were conducted using Stata 12.1® (Stata Corp., College Station, Texas, United States) and stratified by sex, because there is evidence to show that bone mass varies by sex, and an interaction test was significant ($p < 0.1$). Descriptive analysis was based on calculation of relative frequencies and their respective 95% confidence intervals (95%CI) to compare sample subsets comprising participants included and excluded from the analyses (because of losses to follow-up, deaths, or missing data).

Associations between aBMD and conditional growth were analyzed using linear regression and p values were obtained using the Wald test. Results were standardized to enable direct comparisons between regression coefficients. This analysis was conducted with adjusted for mother's educational level, family income, maternal smoking during pregnancy, gestational age, breastfeeding, and skin color. Variables were included in the regressions according to a full adjusted model, irrespective of the level of significance of association with the outcome in bivariate analysis.

Nonlinearity of the relationship between z-scores for each age and bone outcome was evaluated using fractional polynomials. This was followed by visual inspection of dispersion graphs. The linear relationships were considered adequate in all cases except for the variable weight at 18 years of age for males and weight at 11 and 15 years of age for females. The categorical analyses for these variables are shown in the Supplementary Table 1.

Since the first two follow-ups assessed a subset comprising all births with birth weight < 2500 g and a 20% subsample of the remaining children, results were weighted to reproduce the original distribution of the cohort.

3. Results

At 22 years of age, 3810 individuals were followed-up (a follow-up rate of 76.3%). Of these, 3328 cohort members had BMD data, 756 of whom comprised the sample analyzed for this study because they had complete weight and height data from all six previous follow-ups and for the confounding variables used for adjustment. Table 1 describes the participants included in and excluded from the analyses (because of losses to follow-up, death, or missing data), stratified by sex. A total of 421 (55.7%) members of the sample were women. Significant differences between those included and those excluded were observed among the women, for the variables breastfeeding and skin color and gestational age for both sexes.

According to Fig. 1, illustrating the association between CH and aBMD, for men, greater height gain at 4, 11, and 18 years of age was associated with higher whole body aBMD after adjustment for possible confounding factors. The greatest magnitude of increase in aBMD was observed for those who had greatest height gain at 11 years of age (β 0.018 g/cm^2; 95%CI 0.006; 0.030), followed by gain at 4 years of age (β 0.016 g/cm^2; 95%CI 0.005; 0.027), and 18 years of age (β 0.012 g/cm^2; 95%CI 0.002; 0.022). Among the women, aBMD was associated with height gain observed at 1, 4, 11, and 15 years of age. The greatest magnitude of increase in bone density was associated with gain at 4 years of age (β 0.017 g/cm^2; 95%CI 0.007; 0.027), followed by weight gain at 1 (β 0.014 g/cm^2; 95%CI 0.004; 0.024), 11 (β 0.013 g/cm^2; 95%CI 0.004; 0.022), and 15 years of age (β 0.010 g/cm^2; 95%CI 0.001; 0.019).

Fig. 2 describes the effect of CWh on whole body aBMD at 22 years of age. For men, in the adjusted analysis, higher aBMD was observed for those with greater weight gain at 4 (β 0.014 g/cm^2; 95%CI 0.002; 0.026) and at 15 (β 0.015 g/cm^2; 95%CI 0.003; 0.027). With relation to the women, with the exception of birth weight, all of the other weight gain variables were associated with greater bone mass, with highest coefficients for 4 (β 0.025 g/cm^2; 95%CI 0.015; 0.035), 11 (β 0.022 g/cm^2; 95%CI 0.013; 0.031), and 15 years of age (β 0.020 g/cm^2; 95%CI 0.010; 0.030).

4. Discussion

We described associations between height and weight gain at different stages of growth and aBMD in young adult members of a birth cohort. Overall, we observed that greater CH in childhood and adolescence (4, 11, and 18 years of age for men and 1, 4, 11, and 15 years of age for women) was positively associated with aBMD at 22 years of age. With regard to CWh, greater birth weight and weight gain recorded at 4 and 15 years of age among men and at all measurement points except birth in the women, were associated with greater aBMD in early adulthood.

These findings suggest that aBMD is influenced by different critical periods. However, certain methodological challenges interfere with conclusive identification of effects over time [30], such as, for example, when growth measurements are widely separated in time it is difficult to identify the exact growth period of greatest influence [31]. Furthermore, there is also the unknown influence of growth realignment after a previous period of unalignment [30], as is seen among children born with high or low birth weights and lengths, which are frequently compensated by catch-up or catch-down growth during the first 2 years of life [30,32].

Tandon et al. assessed a birth cohort in New Delhi, India, at four points in time (birth, 0–2, 2–11, and 11-adult), finding that greater early growth in length/height (0–2, 2–11, and 11-adult) was associated with higher aBMD at the neck of the femur, the lumbar spine, and the left forearm in adulthood (33–39 years of age), with higher coefficients observed for individuals who gained length/height between 0 and 2 years of age. [16] A study of a subset of elderly women from the Helsinki birth cohort, with assessments at birth and of growth at 0–2, 2–7, and 7–11 years of age, only observed associations between height gain at 0–2 and 2–7 years of age and bone area and bone mineral content (BMC) at the neck of the femur, but even these associations lost significance after adjustment for current height [7]. Kuh et al., analyzed data from a British birth cohort, assessing height gain at the ages of 2–4, 4–7, and 7–15 and weight at 0–2, 2–4, 4–7, 7–15, 15–20, 20–36, and 36–64 years of age, and found that men who had grown most rapidly in height from 4 to 7 years of age had higher hip BMD at 60–64 years of age. With regard to weight, they observed positive associations for gains at 2–4 and 4–7 years of age and at the follow-ups in adulthood among men and an effect that started later among women (at all follow-ups from 7 to 15 years of age) [17].

Some studies have adjusted their analysis models for weight and height variables at the time of bone mass measurement. They suggested that when one observes the disappearance of associations or accentuated attenuation of coefficients after inclusion of these variables, most of the influence lies in the size of the skeletal envelope achieved by adulthood, rather than mineralization [7,16,17]. However, growth in height during childhood cannot be ignored because, for example, it is the primary predictor of adult height and, consequently, to a great extent determines the size of the adult skeleton and its respective bone mass [7,16]. Nevertheless, it is impossible to answer to what extent these correlations between growth, size of the adult body, and bone properties are caused by genes in common that regulate these phenotypes or to adaptations of growth and bone development during childhood, in response to environmental factors [7]. We tested whether body weight was a mediation factor at the time of the bone mass measurement, but this variable was not confirmed as a mediator factor; however, our sample size may have prevented us from finding a more consistent result. In this sense, a recent study with data from the same cohort had evaluated the association between lean and fat mass on bone mineral density at 22 years of age. This publication reveals that although lean and fat mass had both a positive association with bone mass, fat mass had smaller influence than lean mass, suggesting that lean mass is the most important body component for bone density than

Table 1
Characteristics of the cohort members according to inclusion in the conditional height/weight for age analyses, stratified by sex. The 1993 Pelotas Birth Cohort, Brazil.

Variables	*Men*		*Women*	
	Participants included N = 335	Participants excluded[a] N = 2268	Participants included N = 421	Participants excluded[a] N = 2224
	% (95%CI)		% (95%CI)	
Family income (MMW)				
≤1	18.3 (14.1; 22.5)	19.2 (17.6; 20.9)	18.7 (14.9; 22.4)	18.5 (16.8; 20.1)
1.1–3	44.2 (38.8; 49.5)	42.1 (40.0; 44.1)	43.1 (38.3; 47.8)	41.0 (38.9; 43.1)
3.1–6	21.6 (17.1; 26.1)	22.7 (20.9; 24.4)	23.4 (19.4; 27.5)	24.5 (22.7; 26.3)
> 6	15.9 (12.0; 19.9)	16.0 (14.5; 17.6)	14.8 (11.4; 18.3)	16.0 (14.5; 17.6)
Maternal education (years)				
0–4	25.7 (21.0; 30.5)	27.3 (25.4; 29.1)	25.7 (21.5; 29.9)	29.5 (27.6; 31.4)
5–8	49.7 (44.3; 55.1)	46.1 (44.1; 48.2)	49.3 (44.5; 54.1)	45.2 (43.2; 47.3)
9–11	16.8 (12.7; 20.8)	18.3 (16.7; 19.9)	19.0 (15.3; 22.8)	16.8 (15.2; 18.3)
≥12	7.8 (4.9; 10.7)	8.3 (7.2; 9.4)	6.0 (3.7; 8.2)	8.5 (7.3; 9.6)
Maternal smoking in pregnancy				
No	67.8 (62.7; 72.8)	67.6 (65.7; 69.5)	64.1 (59.5; 68.7)	65.9 (63.9; 67.9)
Yes	32.2 (27.2; 37.3)	32.4 (30.5; 34.3)	35.9 (31.3; 40.5)	34.1 (32.1; 36.1)
Gestational age				
< 34	3.0 (1.2; 4.9)	1.3 (0.8; 1.8)	2.9 (1.3; 4.5)	1.7 (1.1; 2.2)
34–36	13.6 (9.9; 17.3)	5.2 (4.3; 6.1)	14.7 (11.3; 18.1)	5.9 (4.9; 6.9)
37–40	71.1 (66.2; 76.0)	76.7 (75.0; 78.5)	70.6 (66.2; 75.0)	79.5 (77.8; 81.2)
> 40	12.3 (8.8; 15.9)	16.8 (15.2; 18.3)	11.8 (8.7; 14.9)	12.9 (11.5; 14.3)
Total duration of breastfeeding (months)				
0.01–1.0	22.4 (17.9; 26.9)	27.5 (21.5; 33.5)	20.7 (16.8; 24.6)	26.0 (19.5; 32.4)
1.01–3.0	30.2 (25.2; 35.1)	33.5 (27.2; 39.8)	26.0 (21.7; 30.2)	37.0 (29.9; 44.1)
3.01–6.0	18.2 (14.1; 22.4)	18.3 (13.2; 23.5)	18.1 (14.4; 21.8)	10.5 (6.0; 15.0)
6.01–12.0	12.8 (9.2; 16.4)	9.2 (5.3; 13.0)	12.6 (9.4; 15.8)	9.9 (5.5; 14.3)
> 12	16.4 (12.4; 20.4)	11.5 (7.2; 15;7)	22.6 (18.6; 26.6)	16.6 (11.1; 22.0)
Skin color				
White	63.9 (58.7; 69.1)	64.4 (62.2; 66.6)	59.4 (54.7; 64;1)	64.8 (62.6; 67.1)
Black, brown or other	36.1 (30.9; 41.3)	35.6 (33.4; 37.8)	40.6 (35.9; 45.3)	35.2 (32.9; 37.4)
Areal bone mineral density (g/cm²) at 22 years	Mean (95%CI) 1.27 (1.26; 1.28)	1.27 (1.26; 1.28)	Mean (95%CI) 1.15 (1.15; 1.16)	1.16 (1.15; 1.16)

N: Number of observations; %: percentage; MMW: monthly minimum wages.
Results were weighted to reproduce the original cohort distribution, considering the early follow-ups included all births < 2500 g and a 20% sample of the remaining children.
[a] Participants excluded from the analyses due to loss of follow-up, death or missing data.

fat mass [33].

It could thus be argued that height, weight, or body mass index (BMI) early on in life do not provide more information on mass and bone density than can be obtained by knowing adult height, weight, and BMI. However, knowing the early trajectories of weight and height enables estimation of future bone mass and bone density [16].

Our analyses were weighted considering that some of the follow-ups assessed a subset of participants comprising all births with birth weight < 2500 g and a 20% subsample of the remaining children. To assess whether associations between height and weight gain at different stages of growth and aBMD among children born with or without low birth weight, additional analyses were performed (Supplementary

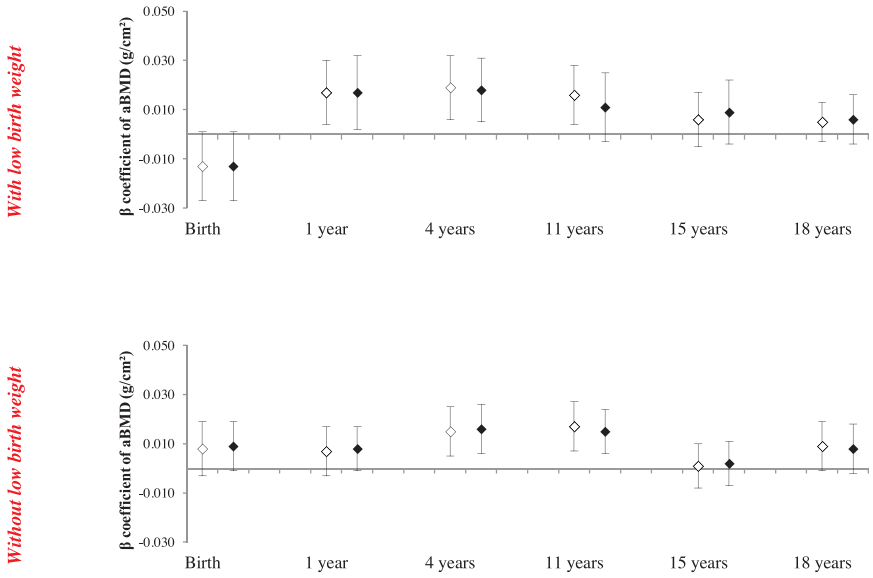

Fig. 1. Regression coefficients and 95% confidence intervals for areal bone mineral density (aBMD) (g/cm²) at 22 years of age according periods of length/height conditional growth among individuals with and without low birth weight. White symbols show crude coefficients and black symbols show adjusted coefficients. The model was adjusted for family income at birth, maternal education, maternal smoking during pregnancy, gestational age, breastfeeding and skin color. For the variable at birth, adjustment for breastfeeding was not included.

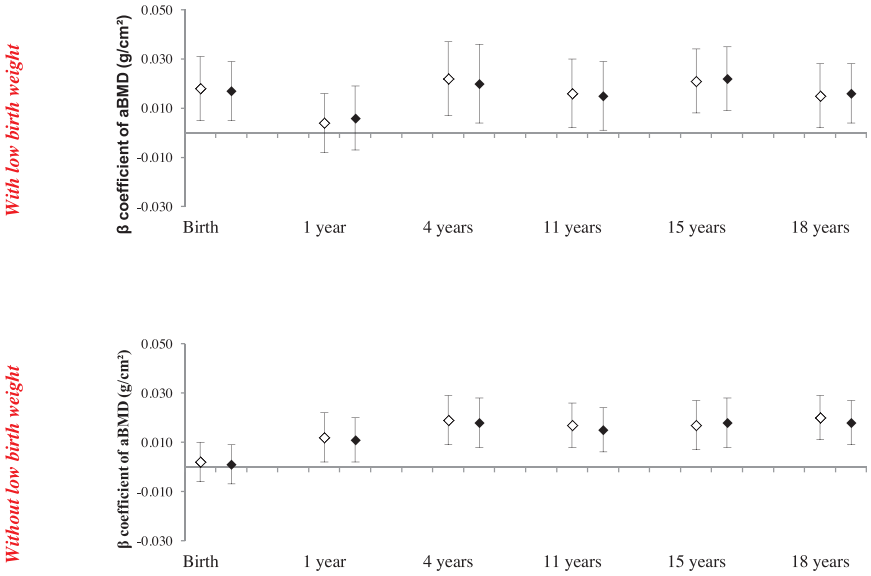

Fig. 2. Regression coefficients and 95% confidence intervals for areal bone mineral density (aBMD) (g/cm^2) at 22 years of age according periods of relative weight conditional growth among individuals with and without low birth weight. White symbols show crude coefficients and black symbols show adjusted coefficients. The model was adjusted for family income at birth, maternal education, maternal smoking during pregnancy, gestational age, breastfeeding and skin color. For the variable at birth, adjustment for breastfeeding was not included.

Figs. 1 and 2). The analyzes showed similar results between birth weight groups.

Our analyses showed that height gain between 4 and 11 years and weight gain from 4 to 15 years are the most important periods for the accumulation of bone mass. Adolescence is a crucial period in development of the skeleton during which approximately half of bone mass is accumulated [34]. Bone mass is acquired at a relatively slow rate throughout childhood. With onset of puberty and the increase in adolescents' growth in height, accumulation of bone mineral mass is rapid, reaching a peak soon after peak height gain. For whole body bone mineral mass, peak bone mineral accrual occurs at 12.5 ± 0.90 years of age in girls and 14.1 ± 0.95 years of age in boys [35]. There is some evidence to support the idea of tracking both for BMC and BMD during growth and maturation. Some studies show that BMC and BMD for the whole body, the hips and the spine measured during prepubescence and postpubescence are correlated (r = 0.54-0.81) with measures obtained 7–8 years later [36–38].

The principal strength of our study is the reliability of the longitudinal weight and height data recorded by trained researchers at all study points. Some limitations should be mentioned. Our study was limited to 18.2% of the original cohort considering that the follow-ups at 1 and 4 years of age were restricted to a subset. However, the baseline characteristics of the subsample were similar to the participants of the main cohort. Long periods between the measurement time points is another limitation in the current study (e.g. 4–11 years). While DXA is the gold-standard method for measurement of bone mass and density, it is subject to certain limitations. Assessment of BMD by DXA without the aid of computed tomography prevents us from assessing other factors that impact on bone strength, such as cortical porosity and thickness, trabecular microstructure and bone geometry [39]. These factors in combination contribute to defining the biomechanical properties of bone tissue, such as rigidity and load supprted [40]. Additionally, increased adiposity is associated with greater measurement error and sometimes with underestimation of bone density because of variability of detection of the interface between soft tissue and bone. [41] On the other hand, the ideal measurement is not possible in many population research scenarios.

5. Conclusions

In conclusion, we demonstrated positive associations between weight and length/weight gain over the course of life and aBMD in young adults of both sexes, with greater evidence especially from 4 to 15 years.

CRediT authorship contribution statement

Isabel Oliveira Bierhals: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Maria Cecília Formoso Assunção:** Conceptualization, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Juliana dos Santos Vaz:** Conceptualization, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Paula Duarte de Oliveira:** Supervision, Visualization, Writing - original draft, Writing - review & editing. **Helen Gonçalves:** Supervision, Visualization, Writing - original draft, Writing - review & editing. **Fernando César Wehrmeister:** Supervision, Visualization, Writing - original draft, Writing - review & editing. **Ana Maria Baptista Menezes:** Supervision, Visualization, Writing - original draft, Writing - review & editing. **Christian Loret de Mola:** Visualization, Writing - original draft, Writing - review & editing. **Caroline Costa:** Visualization, Writing - original draft, Writing - review & editing. **Fernando Celso Barros:** Conceptualization, Supervision, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bone.2019.115088.

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