Effect of Early Life Physical Growth on Midlife Vertebral Dimensions – the Northern Finland Birth Cohort 1966 Study

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ABSTRACT

Small vertebral size is an independent risk factor for osteoporotic vertebral fractures. Physical growth in early life is related to bone health in later life, but the relationship of early growth versus vertebral size has been inconclusively studied. Utilizing the Northern Finland Birth Cohort 1966 with a 47-year follow-up, we investigated how physical growth in early life is associated with midlife vertebral dimensions. We obtained several physical growth parameters of 1) birth (gestational age, length, weight, BMI), 2) infancy and childhood (peak height velocity (PHV), peak weight velocity (PWV), adiposity peak (AP), adiposity rebound (AR)), and 3) puberty (BMI at growth spurt take-off (TO), PHV, height change). We also studied 4) the ages at which AP, AR, pubertal TO and pubertal PHV occurred. The outcome variable, vertebral cross-sectional area (CSA), was obtained from magnetic resonance imaging scans at the mean age of 46.7 years ($n = 517$). Sex-stratified linear regression analyses were used with adjustments for gestational age, smoking, and education. Birth length/weight/BMI, and adult height/weight/BMI were also used as covariates, depending on the model. According to our results, birth weight ($p \leq 0.006$) and infant PWV ($p \leq 0.001$) were positively associated with midlife vertebral CSA among both sexes. Length/height variables were associated with vertebral size only before including adult height in the models, and became non-significant thereafter. Among women, BMI at birth, AP, AR, and pubertal TO were positively associated with midlife vertebral CSA ($p < 0.05$), whereas among men, only high BMI at AR was associated with larger vertebral size ($p = 0.028$). Gestational age or timing of growth were not associated with future vertebral CSA. We conclude that early life weight gain is positively associated with midlife vertebral CSA, and suggest that adult height may mediate the effect of height gain on vertebral size.

KEYWORDS: Osteoporosis, general population studies, magnetic resonance imaging, vertebral size, lumbar spine, aging

1. INTRODUCTION

Osteoporosis is a major global health problem[1] characterized by a significant decline in bone mass and strength[2], and low-energy vertebral fractures are among its most common clinical manifestations[3,4]. A systematic review[5] previously concluded that small vertebral size is an independent risk factor for osteoporotic vertebral fractures, indicating that further knowledge on the factors that affect vertebral size would be beneficial.

Recent reviews[6-8] have shown clear evidence that growth in childhood and puberty is related to bone health in later life. While most publications have focused on bone mineral density (BMD) and bone mineral content (BMC) rather than geometry as outcome measures, some studies have associated growth in early childhood[9,10] and puberty[11,12] with later bone size. However, the interest of these studies has centered on skeletal segments other than the spine.

Data on vertebral size are very scarce. As regards early childhood, a Danish birth cohort study[13] of 44 boys and 64 girls found that the dual X-ray absorptiometry (DXA)-derived bone area of the lumbar spine (L1-L5) at the age of 17 years was associated with birth weight and length, and length at the age of nine months. It was not, however, associated with change in weight or length between birth and age nine months. The results were adjusted for sex. A South African study[14] of 254 boys and 222 girls found no association between the DXA-derived lumbar spine (L1-L4) bone area at the age of 10 years and birth weight, length at the age of one, or weight at the age of one year. The results were adjusted for race, socioeconomic status, bone age, height at the age of 10 years, and weight at the age of 10 years. We could find no published data on the potential relationship

between pubertal growth and vertebral size. Nevertheless, the importance of revealing critical growth periods in terms of long-term bone strength has been emphasized[15].

In this study we aimed to examine how growth in early life is associated with vertebral dimensions in midlife, utilizing the Northern Finland Birth Cohort 1966 study (NFBC1966). We investigated growth parameters including gestational age; birth length, weight, and body mass index (BMI); infant peak height velocity (PHV) and peak weight velocity (PWV); childhood adiposity peak (AP) and adiposity rebound (AR); BMI at pubertal growth spurt take-off (TO); pubertal PHV; and pubertal height change. In addition, we analyzed the ages at which AP, AR, pubertal TO and pubertal PHV occurred. As for vertebral size, we obtained the axial cross-sectional area of the fourth lumbar vertebra (L4) in midlife using magnetic resonance imaging (MRI) scans. We hypothesized that rapid and vigorous growth in early life was associated with larger vertebral size in midlife. We present the expansions for abbreviated growth parameters, alongside other abbreviations, in **Table 1**.

2. MATERIALS AND METHODS

2.1 Initiation and progression of the cohort study

The Northern Finland Birth Cohort 1966 is a prospective population-based cohort study from birth onwards.[16] The population initially consisted of pregnant women living in the two northernmost provinces of Finland (Oulu and Lapland) with expected dates of delivery between Jan 1 and Dec 31, 1966 (n = 12,068 mothers, n = 12,231 children, 96% of all births during 1966 in the area). The cohort participants have been followed since 1966. During childhood and early adolescence, and at the ages of 14, 31 and 46, clinical examinations and questionnaires were used to gather information regarding the participants' health status, medication and lifestyle habits.

2.2 Sample selection of the present study

At the age of 46, NFBC1966 participants with known addresses in Finland (n = 10,321) were invited to fill in a questionnaire and to take part in clinical examinations (attendance rate in both 57%; n = 5,861). Those who attended the clinical examinations and were living in the Oulu region (n = 1,988) were additionally invited to lumbar MRI. The MRI study population consisted of 1,540 participants (77% of those invited to attend the imaging), as 448 participants did not attend due to 1) no show (n = 409), 2) claustrophobia (n = 35), 3) severe obesity preventing the use of the machine (n = 3), or 4) a pacemaker (n = 1). After the imaging, 1,023 participants were further excluded from this study due to 1) difficulties in measuring vertebral dimensions (segmentation error, severe disc degeneration, endplate erosions, presence of spondylodesis or Schmorl's nodes; n = 159), 2) bone-affecting medication (calcium supplements and/or osteoporosis medication; n = 42), and 3) missing growth data (n = 770) or covariate data (n = 52). Therefore, the final eligible population was N = 517 participants (26% of those invited to attend the imaging).

2.3 Assessment of growth

From their birth in 1966 to late puberty, the children's length/height (cm) and weight (g) were measured and documented repeatedly during health care visits (mean 25.7 times, of which 7.4 within the first 18 months). Length/height was measured to the accuracy of 1 cm, and weight was rounded up to the nearest 10 grams. BMI values (kg/m^2) were calculated according to these height and weight measurements.

Growth curves of each individual were based on the repeated height, weight, and BMI measurements. Detailed description of the process is provided elsewhere[17]. The curves in early childhood were fitted using the Reed1 model[18,19], and the JPA2 growth model[20,21] was accordingly used for puberty. These models were chosen as best-fitting after comparisons against other models[17].

The growth curve features which were examined in the present study were chosen according to a previous study[17] utilizing the same NFBC1966 population. Gestational age was calculated as the time difference in weeks between the last menstrual period as reported by the mother, and the birth date of the newborn. Childhood AP and AR (kg/m^2) were determined from the previously well-characterized sex-specific childhood BMI-for-age curves[22,23] as the local maximum and minimum, respectively (**Figure 1**). Age at AP and AR were then obtained from the same curves (**Figure 1**). PHV (cm/year) in infancy and puberty, and PWV (kg/year) in infancy were determined as the local maxima of the height-velocity-for-age and weight-velocity-for-age curves[24], respectively (**Figure 2** for PHVs). Since infant PHV and PWV were reached very early during the neonatal period, specific ages at which they occurred were not recorded. The age at which pubertal PHV occurred was determined from the height-velocity-for-age curve (**Figure 2**). Pubertal growth

spurt TO point was determined as the point just before the pubertal increase in height velocity (**Figure 2**). Estimations of height and weight at the exact point of pubertal TO were obtained using linear interpolation, which was based on the two closest measurements, one before and one after the TO point. Pubertal height change (cm) was calculated as the difference between adult height and height estimation at pubertal TO. All values were independently calculated for each individual.

2.4 Assessment of socioeconomic status, smoking and body mass index at age 46

The number of education years and smoking habits were elicited at the age of 46 using questionnaires. Socioeconomic status, represented by education years, was classified on a three-point scale by the number of years the participant had attended school (≤ 9 years, 9–12 years, >12 years). This was determined by asking two questions: “What is your basic education? 1) Less than nine years of elementary school, 2) elementary school, 3) matriculation examination”; and “What is your vocational education? 1) None, 2) occupational course, 3) vocational school, 4) vocational college, 5) polytechnic, 6) university, 7) other, 8) unfinished course”. Smoking habits were elicited using two questions: 1) “Have you ever smoked cigarettes (yes/no)?” and 2) “Do you currently smoke (yes/no)?” Three categories were formed on the basis of the answers: 1) non-smoker, 2) former smoker, and 3) current smoker. BMI (kg/m^2) at the age of 46 was calculated for each participant using height (m) and weight (kg) values that were systematically measured by a trained study nurse as part of the clinical examinations.

2.5 Lumbar magnetic resonance imaging and vertebral dimensions

We performed MRI scans of the lumbar spine using a 1.5-T imaging system (Signa HDxt, General Electric, Milwaukee, WI) between 2012 and 2014 when the participants were on average 46.7 years old. The imaging sequences followed routine lumbar spine protocol, including T2-weighted fast-recovery fast spin-echo (frFSE) images in sagittal (TR/effTE 3500/112 ms, 4 averages, field of view

280x280 mm, acquisition matrix 448x224, slice thickness 3 mm with 1 mm interslice gap) and transverse planes (TR/effTE 3600/118 ms, 4 averages, FOV 180x180 mm, acquisition matrix 256x224, slice thickness 4 mm with 1 mm interslice gap). We have previously validated the accuracy of MRI in measuring vertebral dimensions[25], although the present scans were not initially implemented for the measurement of vertebral size.

Using the MR images, we measured eight dimensions (cm) from the corpus of L4 to calculate the axial cross-sectional area (CSA) and mean height of L4 (**Figure 3**). Vertebral height dimensions (anterior height, posterior height, minimum height) were measured using the sagittal view and the most medial slice that was available. Width dimensions, i.e. minimum mediolateral width and maximum mediolateral width, were measured using the appropriate axial MRI slices, which varied among participants. Typically, the minimum width was encountered near the middle part of the vertebra, and the maximum width near either the superior or inferior end of the vertebra. Depth dimensions, i.e. anteroposterior dimensions, were measured using axial slices. The superior depth dimension was measured using the most superior appropriate slice just before the intervertebral disc. Correspondingly, the inferior depth dimension was measured using the most inferior slice possible. In order to measure the middle depth dimension, we chose the slice that existed halfway between the superior and inferior ends of the vertebra.

CSA values were calculated using the acknowledged[26] formula: $CSA = \pi * a * b$, where a = vertebral width/2 and b = vertebral depth/2. We used the mean of maximum and minimum mediolateral dimensions as the width dimension, and the mean of superior, inferior and middle anteroposterior dimensions as the depth dimension (**Figure 3**).

The same researcher took all MRI measurements, using NeaView Radiology software (Neagen Oy, Oulu, Finland), version 2.31. The measurements were taken prior to gathering or analyzing any other data on the participants. As described in our earlier report[27], the intra-rater reliability was high, and measurement errors were mild.

2.6 Statistical analyses

We used multivariable linear regression analysis to study our hypothesis that vigorous physical growth in early life is associated with larger vertebral dimensions in midlife. Vertebral size, i.e. the axial CSA of L4 (continuous variable), was regarded as the dependent variable in all analyses. Growth variables, which were all continuous with fairly normal distributions, acted as the explanatory variables. Beta estimates of the explanatory variables were gathered with their 95% confidence intervals.

As vertebral CSA[28] and physical growth patterns[22] were *a priori* known to differ between sexes, all analyses were performed separately for men and women. All models contained adjustments for potential confounders[5,13,29,30]: 1) gestational age, continuous variable; 2) lifetime smoking status determined at 46 years, categorical variable; and 3) socioeconomic status determined by education years, categorical variable. We also used 4) birth length, weight or BMI, continuous variables; and 5) adult height, weight or BMI, continuous variables, determined at 46 years, as covariates in the models, depending on the nature of the explanatory variable.

Length/height were used when analyzing PHVs or pubertal height change, weights were used when analyzing PWVs, and BMIs were used for models with gestational age, AP, AR, BMI at pubertal TO, or age variables. Infant PHV and pubertal PHV were included in the same model, and were thus adjusted for each other. We were unable to include the BMI values of all time points in the

same model, as they were found to be multicollinear (variance inflation factor = 6.5). As a secondary approach, all models were also analyzed without covariates (i.e., with only vertebral CSA and growth data in the models), which enabled us to further include those with missing covariate data (n = 52) in the analyses.

Due to the high exclusion rate, the representativeness of the sample was evaluated. The characteristics of the participants of this study were compared to those of the rest of the cohort ($848 \leq n \leq 11,648$; depending on the variable), which provides the best available estimation of the Northern Finnish population[16]. Chi-squared test was used for categorical variables and the independent-samples t-test was used for continuous variables. Analyses were conducted for both sexes separately. Statistical analyses were conducted using the SPSS software (IBM, Armonk, NY, USA) version 22, 64-bit edition.

2.7 Ethics

The study adheres to the principles of the Declaration of Helsinki with voluntary participation and signed informed consents at each stage. The data were handled on a group level and personal details were replaced by identification codes. The Ethics Committee of the Northern Ostrobothnia Hospital District approved the research.

3. RESULTS

Our sample consisted of 517 participants (44.9% men and 55.1% women) with a mean gestational age of 40.1 (standard deviation 1.9) weeks (**Table 2**). AP was reached before the age of one year among both sexes, and AR occurred between the ages of five and six. In our sample, pubertal growth spurt took off at the age of 9.2 (0.6) years among girls and 11.2 (0.7) years among boys, and height velocity peaked two to three years later. Most participants had attended school for 9–12 years and had never smoked on a regular basis (**Table 2**). MR scans were obtained at the mean age of 46.7 (0.4), and the mean CSA of L4 was 13.3 (1.7) cm² among men and 10.4 (1.3) cm² among women (**Table 2**).

According to the analysis of representativeness, we found some minor differences between our sample and the rest of the cohort. Our sample differed slightly from those excluded in terms of gestational age (40.0 vs. 38.3 weeks in men; 40.1 vs. 38.3 weeks in women) and birth length (50.6 vs. 49.8 cm in men; 50.0 vs. 49.2 cm in women). Our sample also contained less current smokers (17.2 vs. 25.5% in men; 15.6 vs. 19.5% in women) and more people with >12 years of education (25.9 vs. 22.2% in men; 31.2 vs. 30.6% in women) than the rest of the cohort. With regard to the growth variables, the men in our sample differed slightly from those excluded in terms of BMI at AP and the magnitude of infant PHV (18.1 vs. 18.3 kg/m²; 54.9 vs. 54.3 cm/year; respectively). The women in our sample also slightly differed from the rest of the cohort in terms of age of pubertal TO and occurrence of pubertal PHV (9.2 vs. 9.4 years; 11.6 vs. 11.7 years; respectively).

Weight parameters, i.e. birth weight ($p \leq 0.006$) and infant PWV ($p \leq 0.001$) were positively associated with midlife vertebral CSA among both sexes after full adjustments (**Table 3**). All length/height parameters, i.e. birth length, infant PHV, pubertal PHV and pubertal height change, were systematically (i.e. for each variable among both sexes) associated with larger vertebral CSA, but only before adjustment for adult height ($p < 0.05$, data not shown). After adult height was included in the models, all associations became non-significant (**Table 3**).

All BMI parameters, i.e. BMI at birth, AP, AR and pubertal TO, were positively associated with midlife vertebral CSA among women ($p < 0.05$), whereas only high BMI at AR was associated with larger vertebral size in men ($p = 0.029$; **Table 3**). Neither gestational age nor ages at which AP, AR, pubertal TO and pubertal PHV occurred were associated with vertebral CSA among either sex (**Table 3**).

Unadjusted analyses provided identical results to those presented above (data not shown).

4. DISCUSSION

This population-based birth cohort study with a 47-year follow-up enabled us to investigate how physical growth in infancy, early childhood and puberty associated with vertebral dimensions in midlife. Our results showed that birth weight and infant PWV were strong predictors of midlife vertebral CSA among both sexes. Length/height variables were not associated with vertebral size after including adult height in the models. High BMI at birth, AP (indicating a powerful peak), AR (indicating a mild rebound), and pubertal TO were additional predictors of larger midlife vertebral CSA among women, whereas among men, only mild rebound was associated with larger vertebral size. Gestational age and the ages at which AP, AR, pubertal TO and pubertal PHV occurred were not associated with future vertebral CSA among either sex.

Our results indicate that length/height variables were universally associated with midlife vertebral size, but only if adult height was not present in the models. One explanation for this phenomenon may be the connection[15] between adult height, skeletal size, and vertebral size, suggesting that adult height may potentially mediate the effect of early life height gain and height velocity on midlife vertebral size. Among women, high BMI values were associated with larger vertebral size at all time points (i.e. birth, AP, AR and pubertal TO), whereas among men, the only association was detected at AR. This finding suggests that childhood adiposity may be more strongly linked to vertebral size among women than men.

Skeletal growth is associated with the growth of the body[15], and body-weight-dependent skeletal loading is crucial for establishing and maintaining favorable bone qualities[31]. Thus, in terms of the weight-bearing skeleton (including lumbar vertebrae), it is plausible that rapid growers benefit

from their vigorous growth peaks and consequent weight gain. However, in contrast to its potential beneficial effects on skeletal health, it is well-known that vigorous childhood growth and adiposity gains are strong predictors of later-life obesity and serious adiposity-related health consequences such as hypertension, diabetes and stroke [32-34].

Interestingly, some reports[9,13,35,36] have been published on how childhood growth parameters associate more strongly with BMC than BMD in later life. Considering that BMC is the result of bone size and mineral density[37], it has been suggested that early growth predicts future bone size more accurately than mineral density[6]. It has also been further proposed that adult bone size and mineral density have distinct determinants[15], and that the former is primarily affected by growth[36]. Our findings are in line with these hypotheses.

The detailed mechanisms behind the connection between growth patterns and future bone size are incompletely understood. One theory concerns the role of androgens as mediators of growth. In addition to somatotropin and insulin-like growth factors, androgens are among the main regulators of the growth of the body[38,39]. The blood levels of androgenic steroids peak not only in puberty[40] but also in infancy around the occurrence of peak growth velocities[41], and rapid postnatal weight gain has been correlated with increased androgen production in later childhood[42]. As the present study observed weight gain in infancy as being associated with larger later-life vertebral size, the question arises as to whether vertebral growth might be partially mediated by androgen-related hormonal mechanisms.

The main strengths of this study are its well-characterized cohort sample, a five-decade follow-up, and the coverage of several important[6-8] periods of physical growth. Compared to most other

studies[6-8], our follow-up was rather long, which is particularly favorable for a study such as ours on the topic of bone strength and fragility, as the prevalence of osteoporosis peaks in late midlife[2]. Having growth data from infancy, childhood and puberty enabled us to cover several growth periods in our analyses and to evaluate their importance in terms of later-life vertebral health. In addition, our sample size was larger than that of previous studies[13,14], and we were able to investigate the axial cross-sectional area of vertebrae using MRI instead of investigating anteroposteriorly projected DXA-derived vertebral area.

The main limitation of the study was its high exclusion rate (66.4%), which raised concerns of selection bias and, consequently, poor reliability and generalizability of results. Most exclusions resulted from missing growth data ($n = 770$) at any time point during the 47-year follow-up, and a minor group of individuals was excluded due to missing covariate data ($n = 52$). Growth parameters were obtained from growth curves, provided there was one available. This approach meant that we either had all data, or no data whatsoever, regarding an individual's growth. Individuals with no growth data were excluded from all analyses, and those with growth data were included in all analyses, respectively. With regard to missing covariate data, we ran all analyses also in their unadjusted form, which enabled us to include those with missing covariate data ($n = 52$) in the analyses. However, the unadjusted and adjusted models provided identical results, indicating that the acquired increase in sample size did not affect our results.

According to our analysis of representativeness, the present sample was mostly representative of the Northern Finnish population, although notable differences did exist in the percentages of those who were highly educated and those who were current smokers. As the present study required data from birth to midlife and the participation was voluntary at all stages, we believe that the differences are

explained by a lower participation rate of those with lower socioeconomic status. This is a common phenomenon in longitudinal study settings[43-45]. Smoking habits are correlated with socioeconomic status[46], and we believe this is also demonstrated in our sample: we have used both socioeconomic status and smoking habits as covariates in all analyses. The present work is among the first studies to investigate the relation between physical growth and vertebral size to this extent, and further studies are needed to confirm the validity of our results.

Another limitation of the current study was the lack of growth parameters in the period between early childhood and puberty. Although major growth peaks do not typically occur during this period[24], it might also play an important role in determining future vertebral size and strength. In addition to birth weight and infant PWV, obtaining more weight-related growth measures, especially in the period after infancy, might have provided new aspects for the investigation of weight gain and vertebral size throughout childhood and adolescence. However, since the rates of weight gain and adiposity gain in later childhood are affected by non-developmental factors such as overeating, they are not necessarily connected to the physiological growth of the body, and the interpretation of such variables would therefore have been complicated.

We utilized L4 as our vertebra of interest, as it is typically more stable than L5[27]. Even though we have previously demonstrated the high accuracy of MRI in measuring vertebral size[25], it should be noted that the location and orientation of L4 vary between individuals, and this may have affected our orientation of the MRI slices, influencing the measurement error. We had no longitudinal MRI data on the participants' vertebral size, and we were consequently limited to studying associations instead of effects.

In comparison to our earlier investigations[27,47] of lifestyle factors in adolescence, early adulthood and midlife as predictors of vertebral size, we suggest that early life is among the most important periods of life in terms of determining future vertebral size.

We conclude that weight gain in early life is positively associated with vertebral cross-sectional area in midlife. Especially birth weight and infant PWV were strong predictors of future vertebral size among both sexes. The effect of height gain on vertebral size may be connected to adult height. Underlying mechanisms, and the role of early life growth in later vertebral fractures, warrant further studies.

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TABLES

Table 1. Summary of abbreviations.

Abbreviation	Explanation
AP	Adiposity peak
AR	Adiposity rebound
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
effTE	Effective echo time
FOV	Field-of-view
frFSE	Fast-recovery fast spin-echo
L4	Fourth lumbar vertebra
MRI	Magnetic resonance imaging
NFBC1966	Northern Finland birth cohort 1966
PHV	Peak height velocity
PWV	Peak weight velocity
SD	Standard deviation
TO	Growth spurt take-off
TR	Repetition time

Table 2. Characteristics of the MRI population.

	Sample		Excluded ¹	
	Men N = 232 44.9%	Women N = 285 55.1%	Men N = 470 45.9%	Women N = 553 54.1%
Gestational age, weeks; mean (SD)	40.0 (2.0)	40.1 (1.8)		
Age, years; mean (SD)				
At AP	0.8 (0.1)	0.8 (0.1)		
At AR	5.8 (0.8)	5.6 (1.0)		
At pubertal TO	11.2 (0.7)	9.2 (0.6)		
At occurrence of pubertal PHV	13.9 (0.8)	11.6 (0.7)		
At imaging	46.7 (0.4)	46.7 (0.4)	46.8 (0.4)	46.8 (0.4)
Height, cm; mean (SD)				
At birth	50.6 (2.1)	50.0 (1.9)		
At pubertal TO	143.2 (6.5)	132.1 (6.1)		
At 46 years	178.6 (6.3)	164.6 (5.6)	178.7 (6.0)	164.8 (5.8)
Weight, kg; mean (SD)				
At birth	3.5 (0.5)	3.4 (0.5)		
At 46 years	85.6 (12.5)	70.7 (14.3)	86.1 (12.2)	70.7 (13.6)
BMI, kg/m ² ; mean (SD)				
At birth	13.6 (1.4)	13.8 (1.2)		
At AP	18.1 (1.0)	17.8 (1.1)		
At AR	15.4 (1.0)	15.4 (1.1)		
At pubertal TO	17.3 (1.9)	16.6 (2.0)		
At 46 years	26.9 (3.7)	26.5 (5.3)	27.0 (3.6)	26.3 (5.1)
PWV, kg/year; mean (SD)				
In infancy	13.7 (1.8)	12.0 (1.6)		
PHV, cm/year; mean (SD)				
In infancy	54.9 (3.2)	51.1 (3.7)		
In puberty	9.3 (1.4)	7.9 (1.0)		
Pubertal height change, cm; mean (SD)	35.4 (4.8)	32.5 (4.2)		
L4 measurements in midlife				
CSA, cm ² ; mean (SD)	13.1 (1.7)	10.4 (1.3)	13.2 (1.7)	10.6 (1.3)
Vertebral height, cm; mean (SD)	2.8 (0.1)	2.7 (0.1)	2.8 (0.1)	2.7 (0.1)
Education, years; % (N)				
≤9	2.2 (5)	1.4 (4)	3.4 (15)	2.3 (12)
9–12	72.0 (167)	67.4 (192)	72.9 (323)	72.1 (392)
>12	25.9 (60)	31.2 (89)	23.7 (105)	26.7 (140)
Smoking; % (N)				
Non-smoker	50.4 (117)	60.7 (173)	51.0 (224)	59.4 (307)
Former	32.3 (75)	23.5 (67)	32.3 (142)	25.3 (141)
Current	17.2 (40)	15.8 (45)	16.6 (73)	15.2 (79)

¹Those who underwent MRI but were not included in the present analyses; N depends on variable

due to missing data among excluded individuals. AP = Adiposity peak, AR = Adiposity rebound,

BMI = Body mass index, CSA = Cross-sectional area, PHV = Peak height velocity, PWV = Peak weight velocity, SD = Standard deviation, TO = take-off.

Table 3. Results of linear regression models demonstrating how growth parameters in childhood and puberty associate with vertebral axial cross-sectional area in midlife.

	Men		Women	
	β (95% CI)	P value	β (95% CI)	P value
Antenatal period				
Gestational age ^{1,2,§}	-2.1 (-13.7; 9.5)	0.723	-2.5 (-10.8; 5.9)	0.562
Neonatal period and infancy				
Birth length ⁴	5.8 (-5.4; 17.0)	0.306	6.7 (-1.0; 14.4)	0.089
Birth weight ⁶	59.5 (17.1; 101.8)	0.006	81.0 (49.4; 112.5)	<0.001
BMI at birth ²	15.5 (-0.6; 31.6)	0.060	27.4 (14.9; 39.8)	<0.001
Infant PHV ^{3,4,†}	5.0 (-1.8; 11.7)	0.149	1.3 (-2.7; 5.2)	0.531
Infant PWV ^{5,6}	19.0 (8.2; 29.8)	0.001	17.7 (9.4; 26.0)	<0.001
Adiposity peak				
BMI at occurrence ^{1,2}	16.7 (-5.8; 39.1)	0.144	16.0 (1.7; 30.2)	0.028
Age at occurrence ^{1,2}	13.1 (-361.8; 387.9)	0.945	83.1 (-156.5; 322.6)	0.495
Early childhood				
Adiposity rebound				
BMI at occurrence ^{1,2}	29.6 (5.3; 54.0)	0.017	17.8 (3.5; 32.1)	0.015
Age at occurrence ^{1,2}	1.5 (-27.6; 30.6)	0.919	-13.9 (-30.4; 2.7)	0.101
Puberty				
Pubertal take-off				
BMI at occurrence ^{1,2}	3.4 (-9.0; 15.8)	0.592	11.5 (3.4; 19.7)	0.006
Age at occurrence ^{1,2}	-9.3 (-38.3; 19.8)	0.530	5.4 (-18.5; 29.2)	0.658
Pubertal PHV				
Velocity ^{3,4,†}	6.0 (-7.3; 19.2)	0.373	4.1 (-8.8; 16.9)	0.534
Age at occurrence ^{1,2}	-6.8 (-33.1; 19.5)	0.611	-1.5 (-22.9; 19.9)	0.889
Pubertal height change ^{3,4}	2.3 (-1.9; 6.5)	0.279	0.7 (-2.4; 3.8)	0.649

Covariates in all analyses: Gestational age (§not included in its own analysis), smoking, education years. Additional covariates: ¹BMI at birth, ²BMI at 46 years; ³birth length, ⁴height at 46 years; ⁵birth weight, ⁶weight at 46 years. [†]Infant PHV and pubertal PHV were adjusted for each other. β = Beta estimate (mm²), BMI = Body mass index, CI = Confidence interval, PHV = Peak height velocity, PWV = Peak weight velocity.

FIGURE CAPTIONS

Figure 1. Simplified BMI-for-age curve in childhood with its typical[23] characteristics. AP = Adiposity peak, AR = Adiposity rebound.

Figure 2. Typical[24] height-velocity-for-age curve in childhood and adolescence. Simplified. PHV = Peak height velocity.

Figure 3. Measured vertebral dimensions. Sagittal view: Anterior height (Measurement 1), posterior height (Measurement 3), minimum height (Measurement 2). Axial view: Minimum mediolateral width (Measurement 4), maximum mediolateral width (not shown); Depth, i.e. anteroposterior length, superiorly (not shown), halfway (Measurement 5) and inferiorly (not shown). Dashed lines indicate corresponding planes. A = anterior, I = inferior, P = posterior, S = superior direction.

HIGHLIGHTS

- Among NFBC1966, physical growth parameters and vertebral dimensions were studied
- Early-life height gain was positively associated with midlife vertebral CSA
- Height gain was associated with vertebral CSA only before adjustments in the models
- Gestational age or timing of growth were not associated with future vertebral size