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Body Mass Index and its Association with Linear Growth and Pubertal Development

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The authors declare no conflict of interest.

Study Importance

What is already known about this subject?

- Previous studies reported that high body mass index (BMI) correlates positively with linear growth and stature in childhood, but negatively with adolescent linear growth.
- Few prospective cohort studies have addressed the association of BMI with linear growth across the lifecourse from infancy to adolescence, especially among children born in the era of the obesity epidemic (mid-1990s and early 2000's).

What does your study add?

- Our findings from two contemporary prospective birth cohorts with different obesity rates support the role of higher BMI in accelerating linear growth in early life, but earlier pubertal development and slower linear growth during adolescence.
- The relationship of higher BMI in early life with subsequent taller stature was attributable to longer trunks rather than longer legs.

Abstract

Objective: The aim of this study was to investigate the relationship of body mass index (BMI) with subsequent statural growth among children born in the era of the obesity epidemic.

Methods: Among 18,271 children from Belarus (n=16,781, born 1996-1997) and USA (n=1,490, born 1999-2002), we used multivariable linear and ordinal logistic regression to analyze associations of BMI z-score from infancy to adolescence with subsequent standardized length/height velocity, standing height and its components (trunk and leg lengths), and pubertal timing.

Results: The prevalence of early adolescent obesity was 6.2% in Belarus and 12.8% in USA. In both Belarussian and USA children, higher BMI z-scores in infancy and childhood were associated with faster length/height velocity in early life, while higher BMI z-scores during mid-childhood were associated with slower length/height velocity during adolescence. We observed associations with greater standing height, trunk length and earlier pubertal development in adolescence that were stronger for BMI z-scores at mid-childhood than BMI z-scores at birth or infancy.

Conclusions: Our findings in both Belarus and USA support the role of higher BMI in accelerating linear growth in early life (taller stature and longer trunk length), but earlier pubertal development and slower linear growth during adolescence.

Introduction

The current obesity epidemic is a global public health challenge. The increasing prevalence of childhood obesity is a major concern (1), given that excess weight tracks into adulthood (2) and is linked to chronic disorders such as metabolic syndrome, type 2 diabetes, coronary artery disease and stroke (3, 4). Few studies have considered the effects of early life adiposity on stature, which is also known to predict human health and capital (5).

Studies from the 1960's-70's reported that a high body mass index (BMI) in childhood is positively associated with linear growth and stature (6, 7). Recent longitudinal studies in the US (8) and Sweden (9) have observed inverse associations between high BMI-for-age in childhood and linear growth during adolescence. Furthermore, recent evidence suggests a relationship between childhood obesity and the timing of pubertal milestones in boys and girls (10, 11), which is known to influence adolescent linear growth. Previous studies, however, had short follow-up periods, lacked data on linear growth across distinct phases in the lifecourse (infancy, childhood and adolescence) and lacked measures of different components of stature (trunk and leg length). To our knowledge, few prospective cohort studies have addressed the association of BMI with linear growth across the lifecourse from infancy to adolescence, especially among children born in the era of the obesity epidemic (mid-1990s and early 2000's (12)).

To address these gaps, we used prospective cohort data from two countries [USA (Project Viva (13)) and the Republic of Belarus (Promotion of Breastfeeding Intervention Trial; PROBIT (14))] with different childhood obesity rates (15) to examine the relationship of BMI measured from infancy to adolescence to subsequent statural growth velocity, standing height and its components and pubertal timing. We hypothesized that children with higher BMI in both

settings would demonstrate faster linear growth during early life and greater standing height and its components, but earlier pubertal timing and slower linear growth during adolescence.

Methods

Study populations

Project Viva: Project Viva is an ongoing prospective cohort study of pre- and perinatal influences on maternal, fetal and child health. As detailed elsewhere (13), we recruited eligible pregnant women during their first prenatal appointment between April 1999 and November 2002 from obstetric practices at Atrius Harvard Vanguard Medical Associates in eastern Massachusetts. Mothers provided written informed consent at enrollment and follow-up visits, and children provided verbal assent at the mid-childhood and early adolescent visit. The Institutional Review Board of Harvard Pilgrim Health Care approved the project in line with ethical standards established by the Declaration of Helsinki. Of 2,128 live singleton births, in this analysis we studied 1490 (70.0%) children who had at least two measures of weight and length/height between birth and early adolescence.

PROBIT: PROBIT is a cluster-randomized trial of a breastfeeding promotion intervention in the Republic of Belarus, conducted between June 1996 and December 1997 (14). Briefly, 17,046 children were recruited from 31 hospitals that were cluster-randomized to either a control or breastfeeding promotion intervention based on the World Health Organization (WHO) and United Nations Children's Fund Baby-Friendly Hospital Initiative. The trial and subsequent follow-ups were approved by the Belarusian Ministry of Health and received ethical approval from the McGill University Health Centre Research Ethics Board, the Institutional Review Board at Harvard Pilgrim Health Care, and the Avon Longitudinal Study of Parents and Children Law and Ethics Committee. A parent or legal guardian provided written informed consent in

Russian at enrollment and at the follow-up visits, and all children provided written assent at the 11.5- and 16-year visits. Of 17,046 healthy, singleton, term live births, we studied 16,781 (98.5%) children who had at least two measures of weight and stature between birth and mid-adolescence.

Exposure: Body mass index z-score

In Project Viva, trained research assistants measured weight (to the nearest 0.1 kg) and length/height (to the nearest 0.1 cm) using standardized protocols (16, 17) at research visits in infancy (median 6.3; range 5.2–9.8 months), early childhood (3.2; 2.8–6.2 years), mid-childhood (7.7; 6.6–10.9 years) and early adolescence (12.9; 11.9–16.6 years). In PROBIT, polyclinic pediatricians measured weight (to the nearest 0.1 kg) and length/height (to the nearest 0.1 cm) at follow-up visits in infancy (at 1, 2, 3, 6, 9 and 12 months), mid-childhood (6.5; 5.5–8.5 years), early adolescence (11.5; 10.2–14.5 years), and mid-adolescence (16; 14.8–18.9 years), using uniform research specific equipment with standardized training and quality assurance procedures (18).

We used length (<2 years) or standing height (≥2 years) and weight measurements to calculate body mass index (BMI), derive age- and sex-specific BMI z-scores and define underweight, normal weight, overweight and obesity based on the WHO Child Growth Standards (19). We used BMI z-score at the median ages during research visits as our main exposures: Project Viva – birth, 6.3 months, 3.2 and 7.7 years; PROBIT – birth, 3 and 12 months, 6.5 and 11.5 years.

Outcomes

i. <u>*Standardized length/height velocity*</u>*:* Our primary outcome was sex-specific standardized length/height velocity at median follow-up intervals during the research visits: Project Viva –

birth to 6.3 months, 6.3 months to 3.2 years, 3.2–7.7 years and 7.7–12.9 years; PROBIT – birth to 3 months, 3–12 months, 12 months to 6.5 years, 6.5–11.5 years and 11.5–16 years. We first calculated length/height velocity as total length/height change divided by the duration of each time interval described above:

$$v_{1,i} = \frac{(H_i - H_{i-1})}{d_i}$$

where i indexes the research visit, H_i is length/height at research visit i and d_i is the difference in exact age (years) between visit i and i–1.

In PROBIT, we chose the infancy timepoints of 3 and 12 months, which were derived from a cubic spline analysis demonstrating knots with linear changes in length from birth to 3 months and 3 to 12 months. (20). As the time intervals are of unequal duration, we standardized these velocities as z-scores with a mean of 0 and SD of 1:

$$z_{1,i} = \frac{(v_{1,i} - \bar{v}_{1,i})}{SD(v_{i,i})}$$

where $v_{1,i}$ is the length/height velocity between visit i and i–1, $\bar{v}_{1,i}$ is the mean length/height velocity during the same time interval and SD($v_{1,i}$) is the corresponding standard deviation. This approach allowed direct comparison of length/height velocities across different time intervals. We calculated these standardized values using internally derived cohort- and sex-specific means and SDs. While each child's standardized velocity was derived from his or her individual follow-up time, inferences were based on the median follow-up interval.

ii. <u>*Trunk and leg length*</u>*:* At the early adolescent visit in Project Viva and the 11.5-year visit in PROBIT, trained research assistants (in Project Viva) and pediatricians (in PROBIT) measured sitting height using calibrated stadiometers as previously described (21, 22). We

used sitting height as a measure of trunk length and calculated leg length as the difference between standing and sitting height.

iii. *Pubertal development:* In Project Viva, we evaluated pubertal development at the early adolescent visit via a validated written pubertal development scale (PDS) filled out by parents. The PDS has been strongly correlated with physician breast tanner staging in girls (23) and pubic hair staging in boys (24). PDS questions for boys include 4 items: voice deepening, facial and body hair growth, acne, and growth spurt. PDS questions for girls include 5 items: breast development, body hair growth, acne, growth spurt and menarche. The response options for each item (except for menarche) were: "not yet started" (1 point), "barely started" (2 points), "definitely started" (3 points), "seems complete" (4 points) and "I don't know" (coded as missing). A "yes" answer on the menarche question receives 4 points, while a "no" answer receives 1 point. We derived a pubertal score for each participant by summing the point values and averaging across all items as detailed previously (25). In PROBIT, pediatricians received special training to assess genital development in boys, breast development in girls and pubic hair development in boys and girls at 11.5 years (range 10.2–14.5 years), using Tanner's criteria for stage of maturation (stages 1 to 5) (26, 27). We also obtained self-reported pubic hair Tanner staging through pictograph questionnaires in early adolescence in Project Viva and at 16 years (range 14.8–18.9 years) in PROBIT.

Statistical analysis

We used multivariable linear regression to examine associations of BMI z-score (or overweight/obesity) at each exposure timepoint with the following outcomes: length/height velocities at subsequent time intervals; standing height, and trunk and leg length in adolescence. In both cohorts, we adjusted for maternal age, gestational age at delivery, parental height and

BMI as continuous variables and parental educational attainment as a categorical variable (non-university- or university-educated). In Project Viva, we additionally adjusted for maternal smoking history (never, smoked prior to pregnancy or smoked during pregnancy), parity (nulliparous or multiparous), breastfeeding initiation (yes or no) and child race/ethnicity (white, black, Hispanic, Asian or others) as categorical variables. In PROBIT we additionally adjusted for maternal smoking during pregnancy (yes or no) and geographic region of residence (east rural, east urban, west rural or west urban) as categorical variables. We selected these covariates based on prior publications linking BMI and linear growth (6, 9, 28, 29).

In all models, we adjusted for BMI z-score in all previous age periods, but not in subsequent age periods. In models with length/height velocity as the outcome, we also adjusted for length/height velocities prior to BMI at each exposure timepoint (for example: associations between BMI z-score at 3 months and length/height velocity at 3–12 months were adjusted for length/height velocity at 0–3 months). Additionally, we used multivariable ordinal logistic regression, adjusting for the covariates listed, to examine associations of BMI z-score at each timepoint with pubertal development at early- and mid-adolescence.

For all PROBIT analyses, we accounted for clustered measurements within hospitals/polyclinics by including a random effect term for hospital/polyclinic. We did not adjust for intervention vs. control arms, as earlier analyses showed no differences in height at childhood and adolescence between the two study arms (30). We decided *a priori* to conduct all analyses separately in boys and girls, given the known sex differences in linear growth.

We used chained equation multiple imputation to impute values for children with missing covariate and outcome data, generating 50 imputed data sets including all participants with live births. The imputation model included all exposures, outcomes and covariates under study. In

final analytic models after imputation, we combined imputed data sets using MI ESTIMATE in Stata after excluding participants without at least one outcome measure. Lastly, to assess robustness of our study findings, we repeated all analyses in subjects without missing covariate data. We analyzed all data using Stata version 15 (StataCorp, Texas, USA).

Results

Cohort descriptions

Compared to mothers from PROBIT, mothers from Project Viva were older (mean 32.7 vs. 24.5 years) and primarily university-educated (73.5% vs. 13.9%) (**Table 1**). The prevalence of early adolescent obesity was 6.2% (at 11.5 years) in PROBIT and 12.8% (at 12.9 years) in Project Viva. Compared to boys, girls had slower length/height velocities during infancy and adolescent periods, shorter heights and longer trunks in early adolescence, and earlier pubertal development in early adolescence (**Tables 2–3**).

Associations of BMI z-score with subsequent length/height velocity

In PROBIT, higher BMI z-scores at birth, 3 and 12 months were more strongly associated with length/height velocity at the next interval (i.e., at 0–3, 3–12 months and 12 months–6.5 years respectively) than at later intervals. For example, in boys, a 1-SD increase in BMI z-score at 3 months was associated with increases in length/height velocity of 0.11 SD units (95% CI 0.09,0.13) at 3–12 months, 0.04 SD units (0.01,0.06) at 12 months–6.5 years and 0.03 SD units (0.00,0.05) at 6.5–11.5 years (**Figure 1A**). Similarly in Project Viva, a higher BMI z-score at 6.3 months was more strongly associated with length/height velocity at 6.3 months to 3.2 years than at 3.2–7.7 or 7.7–12.9 years (**Figure 1B**).

In PROBIT, higher BMI z-scores at 6.5 years was positively associated with height velocity at 6.5–11.5 years, but negatively associated with height velocity at 11.5–16 years

(**Figure 1A**). A similar observation was noted in Project Viva: a higher BMI z-score at 3.2 years was positively associated with height velocity at 3.2–7.7 years (0.18 units; 0.08,0.28) but negatively associated with height velocity at 7.7–12.9 years (-0.14 SD units; -0.25,-0.03) in girls (**Figure 1B**).

Associations of BMI z-score with standing height, trunk and leg length

In PROBIT, associations with standing height at 11.5 years were stronger for BMI z-scores at 6.5 years than at birth or 3 or 12 months: for example, in girls, a 1-SD higher BMI z-score at 6.5 years was more strongly associated with standing height (1.64 cm; 1.46, 1.81) than was BMI z-score 12 months (0.27 cm; 0.07, 0.46) (**Table 4**). Similar results were observed in Project Viva: for example, in girls, a 1-SD higher BMI z-score at 7.7 years was more strongly associated with standing height at 12.9 years (1.14 cm; 0.43, 1.85) than was BMI z-score at 6.3 months (0.31 cm; -0.25, 0.87) (**Table 5**). Furthermore in PROBIT, the associations of BMI z-scores with standing height at 16 years were weaker than at 11.5 years (**Table 4**) and appear to be partly mediated by pubertal development at 11.5 years. For example, in girls, a 1-SD higher BMI z-score at 6.5 years was positively associated with standing height at 16 years (0.10 cm; -0.05, 0.25), which was attenuated when adjusted for breast development (0.03 cm; -0.13, 0.18) or pubic hair stage (0.04 cm; -0.12, 0.19) at 11.5 years (**Table S1**).

In PROBIT, associations of BMI z-scores with trunk length at 11.5 years were stronger than associations with leg length: for example in girls, a 1-SD increase in BMI z-score at 6.5 years was more strongly associated with trunk length (1.18 cm; 1.08, 1.29) than leg length (0.45 cm; 0.34, 0.56) at 11.5 years. We noted similar observations in Project Viva: for example in girls, a 1-SD increase in BMI z-score at 7.7 years was more strongly associated with trunk length (0.88 cm; 0.44, 1.32) than leg length (0.26 cm; -0.20, 0.72) at 12.9 years.

Associations of BMI z-score with pubertal development

In PROBIT, children with higher BMI z-scores demonstrated more advanced genital (for boys), breast (for girls) and pubic hair development at 11.5 years. These associations were generally stronger for BMI z-scores at 6.5 years than at birth, 3 or 12 months (**Table 4**). Similarly in Project Viva, associations with pubertal score and pubic hair development at 12.9 years were stronger for BMI z-score at 7.7 years than at birth or 6.3 months (**Table 5**). Furthermore in PROBIT, the associations of BMI z-scores with pubic hair development at 16 years were weaker than with pubic hair development at 11.5 years.

Associations of overweight or obesity with length/height velocity, standing height trunk and leg length and pubertal development

Our findings for overweight or obesity showed similar patterns of associations to those of BMI z-score, i.e., children who were overweight or obese (vs. those who were of normal weight or underweight) had accelerated linear growth in early life, with taller stature and longer trunks, but earlier pubertal development and slower linear growth during adolescence (**Tables S2–S5**).

Complete case analyses

Our complete case analyses in both cohorts showed similar patterns of associations of BMI z-score with length/height velocity (**Figure S1A–B**), standing height, trunk and leg length and pubertal development (**Tables S6–S7**) as those observed after multiple imputation.

Discussion

We found that in both cohorts, children with higher BMI during infancy and childhood demonstrated faster subsequent growth in stature, both for standing height and trunk length. Additionally, children with higher BMI showed earlier pubertal development and slower linear

growth during adolescence; these associations were more pronounced for BMI measures in later childhood than in infancy.

Few prospective cohort studies have addressed the relationship of BMI with statural growth across the lifecourse from infancy to adolescence. The associations we observed between higher BMI during early life and subsequent increase in length/height velocities corroborate the findings from population-based studies by He *et al* (28) and Luo *et al* (29). These studies, however, lacked data on linear growth during early life (<2 years of age) and were based on children born and raised in the 1970s, a time period before the obesity epidemic began and when environmental factors were relatively favorable for growth (28).

Our findings therefore better reflect contemporary children born and raised in the mid-1990s and early 2000's, when the obesity epidemic was accelerating (12). Furthermore, we found consistent results in both cohorts, despite having different obesity rates (6.2% at 11.5 years in PROBIT, and 12.8% at 12.9 years in Project Viva) and exposures to obesogenic environments. They therefore add support to the notion that high BMI is associated with an accelerated rate of linear growth in early life (31). We speculate that factors known to influence linear growth and previously shown to be positively correlated with BMI, such as insulin-like growth factor I (IGF-I) (32) and fasting insulin (33), may play an important role in the relationship between higher BMI in early life and accelerated subsequent linear growth.

As a consequence of faster linear growth, pre-pubescent children with obesity typically present with taller stature than their normal-weight peers (34), consistent with our observations of larger standing heights during early adolescence among children with higher BMIs during mid-childhood. Furthermore, the greater heights in early adolescence were mainly attributable to longer trunks, rather than longer legs. To our knowledge, only one previous study has reported

associations between greater fatness and subsequent longer trunks in prepubescent children (35). Previous findings in pre-pubertal children showed that IGF-I had stronger associations with later growth in trunk, but not leg length (36). Other studies also reported that pre-pubertal BMI is associated with insulin-induced reduction of sex hormone binding globulin and increased sex steroid bioavailability, which has a marked influence on the growth hormone–IGFI axis (37). We speculate that the divergence in components of later height among children with high BMI may be due to differences in exposure to hormonal determinants of femoral and vertebral growth i.e., sex steroids and IGF-I (36, 37). The divergence in height components may have unintended consequences. We have previously shown that trunk length, compared to leg length, had stronger associations with blood pressure and cardio-metabolic risk in mid-childhood independently of BMI (22). A low leg-to-trunk ratio has also been associated with an elevated risk of hypertension in children and adolescents (38).

Previous studies have shown that children with higher pre-pubertal BMI have a smaller pubertal height gain (9), consistent with our findings of slower adolescent growth in stature among pre-pubescent children with higher BMI. As noted in our observations and in other studies (39), higher pre-pubertal BMI is associated with earlier pubertal development, possibly through increased secretion of adipokines (e.g., leptin) that may trigger activity of the gonadotrophin-releasing hormone pulse generator (10). In addition, some genetic signals may influence both BMI and pubertal development (40). Earlier pubertal development typically leads to earlier cessation of linear growth and, therefore, smaller adolescent height gains. More recently, Lee *et al* reported correlations of delayed pubertal development with obesity in boys (41), although that study was cross-sectional and based on a convenience sample. Furthermore,

for Project Viva, we speculate that the observed sex differences in early adolescent linear growth might be due to the fact that girls were further along in puberty than boys at early adolescence.

Although we lacked data on final adult height in both cohorts, we observed weaker associations (which were mostly null) between childhood BMI and height at 16 years in PROBIT children. This finding is consistent with recent evidence suggesting that children with high BMI eventually attain the same final height as their normal-weight peers (9). We acknowledge that childhood overweight and obesity have more serious health consequences (such as metabolic syndrome, type 2 diabetes, coronary heart disease and stroke later in life (2-4)) than deviations in linear growth and stature. Nevertheless, these deviations are a limiting factor to "optimal" body growth which may have consequences for future health outcomes (22).

Strengths of our study include its relatively large sample size of over eighteen thousand children from two prospective cohorts, each with multiple measures of growth from infancy to adolescence obtained by highly-trained research staff. In addition, our study benefits from the fact that we obtained similar results in two very different populations with differing obesity rates (15) and confounding structures (degree of income inequality, health care systems), suggesting that bias due to uncontrolled (residual) confounding is an unlikely explanation for the associations we observed.

Our study is not without limitations, however. First, BMI is an imperfect measure of adiposity; increased BMI is linked with maturational status, driven by gains in bone and muscle as well as fat. Thus, our results may not reflect the true relationship between adiposity and subsequent linear growth. Second, the use of BMI is currently not recommended for children below age 2 years; rather, weight-for-length (WFL) is recommended as a marker of weight status and adiposity for children in this age group (42). Past studies, however, have identified high

concordance between WFL and BMI in infancy (43). Furthermore, we have previously shown that choice of WFL or BMI as indicators of overweight in children younger than 2 years does not substantially affect the ability to estimate future adiposity and other cardio-metabolic outcomes (15). These observations suggest that the use of BMI is likely to yield comparable results to those of WFL for children below age 2. Third, we lacked indicators of growth tempo (i.e., age at peak height velocity) and skeletal maturation (i.e., bone age). Fourth, we used self-reported measures of pubic hair staging and parent-reported measures of pubertal score in Project Viva, which may be subject to measurement error. Nevertheless, both pubertal indicators were reasonably correlated with each other (Spearman's rank correlation = 0.66) and showed similar associations with BMI z-score, suggesting reliability of the reported pubertal measures. Fifth, we investigated multiple outcomes, thereby increasing the risk of false-positive results. We chose not to adjust for multiple comparisons. Instead, the "significance" of our findings is based on the strength and consistency of the associations observed across related outcomes and between the two cohorts (44). Lastly, our study findings may not be generalizable to other populations, since many of our participants were white (both cohorts) or university-educated (in Project Viva). Differences between children who continued vs those lost to follow-up may theoretically have led to selection bias, although our multiple imputation analyses showed very similar findings to those of our complete-case analyses.

Conclusion

In conclusion, our findings from two contemporary prospective birth cohorts with different obesity rates support the role of higher BMI in accelerating linear growth in early life, with taller stature and longer trunk length, but earlier pubertal development and slower linear growth during adolescence.

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Figure Legends

Figure 1: Associations of child BMI z-score with standardized length/height velocity in (**A**) PROBIT and (**B**) Project Viva.

Table 1: Maternal and paternal characteristics of participating children in PROBIT and Project Viva

	PROBIT n=12,206[a]	**Project Viva n=1,311[a]**
Maternal age	24.5 (4.9)[b]	32.7 (4.6)
Maternal smoking history		
Never smoked	12009 (98.4)[b]	928 (70.8)
Smoked before pregnancy	–[c]	271 (20.7)
Smoked during pregnancy	197 (1.6)	112 (8.5)
Parity		
Nulliparous	–	627 (47.8)
Multiparous	–	684 (52.2)
Maternal education level		
Not university educated	10509 (86.1)	347 (26.5)
University educated	1697 (13.9)	964 (73.5)
Paternal education level		
Not university educated	10583 (86.7)	418 (31.9)
University educated	1623 (13.3)	893 (68.1)
Maternal height (cm)	164.4 (5.6)	165.1 (7.0)
Maternal BMI (kg/m^2)	24.5 (4.4)	24.7 (5.2)
Paternal height (cm)	176.1 (6.6)	179.5 (7.5)
Paternal BMI (kg/m^2)	25.7 (3.3)	26.5 (3.9)
Gestational age at delivery (weeks)	39.4 (1.0)	39.5 (1.8)
Child race/ethnicity		
White	12206 (100)	916 (69.9)
Black	–	159 (12.1)
Hispanic	–	50 (3.8)
Asian	–	50 (3.8)
Others	–	136 (10.4)
Breastfeeding initiation		
No	–	123 (9.4)
Yes	–	1183 (90.6)
Geographic region		
East urban	3715 (30.4)	–
East rural	1971 (16.2)	–
West urban	2960 (24.3)	–
West rural	3560 (29.2)	–

[a] Sample sizes restricted to subjects with at least one outcome measure and no missing covariates.
[b] Mean (SD) for continuous variables or n (%) for categorical variables.
[c] Data not available.

Table 2: Growth and pubertal characteristics of children in PROBIT

	Boys		Girls	
	n[a]	Mean (SD) or %	n[a]	Mean (SD) or %
BMI z-score (SD units)				
0m	8682	-0.54 (0.93)	8099	-0.64 (0.95)
3m	8602	-0.21 (1.04)	8022	-0.13 (0.94)
12m	8509	1.14 (0.96)	7932	1.14 (0.88)
6.5y	7172	0.12 (1.05)	6702	-0.05 (0.97)
11.5y	7105	0.20 (1.17)	6738	-0.05 (1.14)
16y	6918	0.12 (1.02)	6534	0.00 (0.94)
Obesity at 11.5y	565	8.0	290	4.3
Obesity at 16y	318	4.6	160	2.5
Length/Height velocity (cm/y)				
0–3m	8606	37.1 (9.6)	8024	34.9 (8.9)
3–12m	8475	19.9 (3.6)	7886	20.0 (3.4)
12m – 6.5y	7155	7.9 (0.8)	6688	8.0 (0.8)
6.5–11.5y	6634	5.6 (0.9)	6311	6.1 (1.0)
11.5–16y	6509	5.9 (1.3)	6188	3.2 (1.4)
Outcomes at 11.5 years				
Standing height (cm)	7123	149.0 (7.6)	6750	150.7 (7.9)
Trunk length (cm)	7111	77.5 (4.2)	6744	78.8 (4.6)
Leg length (cm)	7111	71.5 (4.9)	6744	71.8 (4.8)
Genital development at 11.5 years				
Stage 1	948	13.4	–[b]	–
Stage 2	3818	54.0	–	–
Stage 3	2047	28.9	–	–
Stage 4	240	3.4	–	–
Stage 5	21	0.3	–	–
Breast development at 11.5 years				
Stage 1	–	–	767	11.5
Stage 2	–	–	3441	51.4
Stage 3	–	–	2149	32.1
Stage 4	–	–	302	4.5
Stage 5	–	–	35	0.5
Pubic hair development at 11.5 years				
Stage 1	3553	50.2	1871	28.0
Stage 2	2895	40.9	3142	46.9
Stage 3	571	8.1	1491	22.3
Stage 4	47	0.7	175	2.6
Stage 5	8	0.1	15	0.2
Outcomes at 16 years				
Height (cm)	6948	175.7 (7.0)	6489	164.9 (6.1)
Pubic hair development at 16 years				
Stage 1	16	0.2	101	1.6
Stage 2	51	0.7	578	8.9
Stage 3	466	6.8	1981	30.5
Stage 4	2700	39.2	2064	31.8
Stage 5	3651	53.0	1777	27.3

[a] Sample sizes restricted to subjects with at least one outcome measure

[b] Data not available.

Table 3: Growth and pubertal characteristics of children in Project Viva.

	Boys		Girls	
	n[a]	**Mean (SD) or %**	**n[a]**	**Mean (SD) or %**
BMI z-score (SD units)				
Birth	418	0.54 (0.98)	442	0.61 (0.93)
6.3m	559	0.70 (1.08)	544	0.63 (0.97)
3.2y	603	0.80 (0.97)	590	0.62 (0.94)
7.7y	542	0.61 (1.21)	539	0.54 (1.13)
12.9y	521	0.60 (1.23)	513	0.45 (1.25)
Obesity at 12.9y	70	13.4	62	12.1
Length/Height velocity (cm/y)				
Birth to 6.3m	350	32.3 (3.9)	364	30.7 (4.1)
6.3m – 3.2y	473	11.2 (1.1)	465	11.4 (1.1)
3.2 – 7.7y	483	6.7 (0.7)	492	6.7 (0.7)
7.7 – 12.9y	450	6.0 (0.9)	447	5.9 (0.9)
Outcomes at 12.9y				
Standing height (cm)	523	160.8 (10.1)	514	158.9 (7.4)
Trunk length (cm)	522	82.1 (5.6)	513	82.8 (4.2)
Leg length (cm)	522	78.7 (5.9)	513	76.1 (4.6)
Pubertal score	584	2.2 (0.7)	552	2.9 (0.7)
Pubic hair development at 12.9y				
Stage 1	21	3.9	12	2.4
Stage 2	85	15.9	52	10.3
Stage 3	149	27.8	118	23.3
Stage 4	203	37.9	188	37.2
Stage 5	78	14.6	136	26.9

[a] Sample sizes restricted to subjects with at least one outcome measure

Table 4: Associations of BMI z-score with standing height, trunk and leg length, and pubertal development at 11.5 and 16 years in PROBIT

	β (95% CI)[a]				OR (95% CI)[a,b]		
	11.5y			16y	11.5y		16y
BMI z-score	**Standing height (cm)**	**Trunk length (cm)**	**Leg length (cm)**	**Standing height (cm)**	**Genital development**	**Pubic hair stage**	**Pubic hair stage**
Boys (n=8,682)							
0m	**0.39 (0.22,0.56)[c]**	**0.23 (0.13,0.33)**	**0.16 (0.05,0.28)**	**0.56 (0.40,0.73)**	1.05 (1.00,1.12)	1.03 (0.97,1.09)	1.02 (0.96,1.08)
3m	0.12 (-0.03,0.26)	**0.11 (0.03,0.20)**	0.00 (-0.09,0.10)	-0.01 (-0.16,0.13)	1.05 (1.00,1.10)	**1.09 (1.04,1.14)**	1.06 (1.00,1.11)
12m	**0.30 (0.13,0.46)**	**0.27 (0.17,0.37)**	0.03 (-0.08,0.14)	0.14 (-0.02,0.30)	1.05 (1.00,1.11)	**1.10 (1.04,1.16)**	1.03 (0.98,1.09)
6.5y	**1.37 (1.22,1.52)**	**1.03 (0.94,1.12)**	**0.34 (0.24,0.45)**	**0.27 (0.12,0.42)**	**1.19 (1.13,1.26)**	**1.26 (1.19,1.33)**	**1.10 (1.05,1.16)**
11.5y	**1.63 (1.46,1.80)**	**1.14 (1.05,1.24)**	**0.49 (0.38,0.61)**	**0.29 (0.12,0.46)**	**1.29 (1.22,1.37)**	**1.43 (1.35,1.52)**	**1.21 (1.15,1.28)**
16y	—	—	—	0.04 (-0.16,0.25)	—	—	**1.23 (1.15,1.32)**
Girls (n=8,099)					**Breast development**		
0m	**0.36 (0.18,0.54)**	**0.16 (0.05,0.27)**	**0.20 (0.08,0.31)**	**0.53 (0.38,0.68)**	1.00 (0.94,1.05)	0.97 (0.92,1.03)	0.98 (0.93,1.04)
3m	0.03 (-0.15,0.21)	**0.14 (0.03,0.25)**	-0.11 (-0.22,0.01)	-0.07 (-0.21,0.08)	**1.08 (1.02,1.14)**	**1.11 (1.05,1.17)**	1.04 (0.99,1.10)
12m	**0.27 (0.07,0.46)**	**0.24 (0.12,0.36)**	0.03 (-0.10,0.15)	0.03 (-0.13,0.19)	**1.11 (1.05,1.18)**	**1.15 (1.08,1.21)**	1.01 (0.96,1.07)
6.5y	**1.64 (1.46,1.81)**	**1.18 (1.08,1.29)**	**0.45 (0.34,0.56)**	0.10 (-0.05,0.25)	**1.65 (1.56,1.75)**	**1.54 (1.46,1.63)**	**1.07 (1.02,1.13)**
11.5y	**1.63 (1.44,1.81)**	**1.26 (1.15,1.37)**	**0.37 (0.25,0.49)**	-0.13 (-0.29,0.04)	**2.22 (2.09,2.37)**	**1.89 (1.78,2.00)**	**1.08 (1.02,1.14)**
16y	—	—	—	**-0.50 (-0.69,-0.30)**	—	—	**1.09 (1.03,1.16)**

[a] Adjusted for maternal and paternal education level, height and BMI; maternal age and smoking during pregnancy; gestational age at delivery; geographic region; BMI z-score at all previous time points and age at outcome.

[b] OR (odds ratio) reflects relative odds of being in a higher Tanner stage category.

[c] Bold values indicate statistically significant associations at $p<0.05$.

Table 5: Associations of BMI z-score with standing height, trunk and leg length, and pubertal development at 12.9 years in Project Viva

	β (95% CI)[a]				OR (95% CI)[a,b]
BMI z-score	**Standing height (cm)**	**Trunk length (cm)**	**Leg length (cm)**	**Pubertal score (units)**	**Pubic hair stage**
Boys (n=758)					
Birth	0.09 (-0.69,0.88)	0.21 (-0.26,0.69)	-0.12 (-0.62,0.38)	-0.02 (-0.09,0.06)	1.03 (0.83,1.27)
6.3m	0.32 (-0.27,0.92)	0.34 (-0.02,0.70)	-0.01 (-0.39,0.36)	0.03 (-0.02,0.09)	1.11 (0.93,1.32)
3.2y	**0.88 (0.10,1.67)[c]**	**0.77 (0.31,1.22)**	0.12 (-0.39,0.63)	0.01 (-0.05,0.08)	0.93 (0.75,1.16)
7.7y	**1.62 (0.84,2.40)**	**0.71 (0.24,1.19)**	**0.91 (0.39,1.42)**	**0.11 (0.05,0.18)**	**1.49 (1.19,1.87)**
12.9y	0.91 (-0.01,1.82)	**1.17 (0.63,1.71)**	-0.27 (-0.85,0.32)	**0.12 (0.04,0.20)**	**1.37 (1.04,1.79)**
Girls (n=732)					
Birth	0.03 (-0.72,0.79)	-0.05 (-0.51,0.42)	0.08 (-0.39,0.55)	-0.02 (-0.09,0.04)	1.05 (0.84,1.31)
6.3m	0.31 (-0.25,0.87)	**0.41 (0.05,0.77)**	-0.10 (-0.47,0.27)	0.05 (-0.01,0.10)	1.28 (1.05,1.56)
3.2y	0.59 (-0.14,1.31)	0.72 (0.27,1.17)	-0.13 (-0.59,0.32)	0.05 (-0.01,0.12)	1.09 (0.86,1.37)
7.7y	**1.14 (0.43,1.85)**	**0.88 (0.44,1.32)**	0.26 (-0.20,0.72)	**0.17 (0.10,0.24)**	**1.60 (1.26,2.03)**
12.9y	**1.43 (0.60,2.27)**	**1.50 (0.98,2.03)**	-0.07 (-0.60,0.46)	**0.30 (0.23,0.38)**	**1.84 (1.38,2.45)**

[a] Adjusted for maternal and paternal education level, height and BMI; maternal age, smoking history and parity; gestational age at delivery; breastfeeding initiation; child ethnicity; BMI z-score at all previous time points and age at outcome.

[b] OR (odds ratio) reflects relative odds of being in a higher Tanner stage category.

[c] Bold values indicate statistically significant associations at $p<0.05$.