Adipose and Height Growth Through Childhood and Blood Pressure Status in a Large Prospective Cohort Study

Alexander Jones, Marietta Charakida, Emanuela Falaschetti, Aroon D. Hingorani, Nicholas Finer, Stefano Masi, Ann E. Donald, Debbie A. Lawlor, George Davey Smith, John E. Deanfield

Abstract—Raised blood pressure (BP) is the world’s leading mortality risk factor. Childhood BP substantially predicts adult levels, and although both prenatal and postnatal growth influence it, their relative importance is debated. In a longitudinal study (Avon Longitudinal Study of Parents and Children) of 12,962 healthy children, we aimed to assess the relative contribution of different growth periods and of standardized measures of height versus weight-for-height (an adiposity marker) to BP at age 10 years. Conditional growth modeling was used in the 3230 boys and 3346 girls with BP measurements. Systolic BP was inversely associated with birth weight and weight-for-height but not length (−0.33, −0.27, and −0.12 mm Hg · SD−1; P=0.003, 0.035, and 0.35, respectively). In infancy, weight, weight-for-height, and height gains were all positively associated with systolic BP (0.90, 0.41, and 0.82 mm Hg · SD−1, respectively; all P<0.001). After infancy, all of the growth modalities were positively associated with systolic BP (weight, 1.91; weight-for-height, 1.56; height, 1.20 mm Hg · SD−1; all P<0.001). Similar but weaker associations were found with diastolic BP. Although BP at 10 years was associated with both prenatal and early postnatal growth, their influence was small compared with that of later growth. Because BP ranking relative to the population is substantially determined in the first decade of life, a focus on strategies to reduce the development of adiposity from infancy onward, rather than an emphasis on the nutrition and weight of mothers and infants, should bring greater reductions in population BP. (Hypertension. 2012;59:919-925.) ● Online Data Supplement

Key Words: blood pressure ■ childhood growth ■ hypertension ■ obesity ■ population

Raised blood pressure (BP) is the world’s leading mortality risk factor, responsible for 13% of deaths. Effects of BP are continuous across its normal range and not limited to hypertensives. Therefore, the greatest population health benefit should come from preventative strategies that reduce population-wide BP rather than targeting individuals with hypertension. BP ranking relative to the population is substantially determined in the first decade, suggesting that effective prevention strategies should begin in early childhood.

Both genetic and environmental factors contribute to raised BP, and there is considerable interest in the role of growth and habitus. Worldwide prevalence of childhood obesity has increased dramatically over recent decades, affecting cardiovascular (CV) risk adversely. Because the relative importance of growth in height compared with adiposity for later BP remains unclear, we examined the associations of BP with these types of growth during different phases of childhood.

Controversy remains over how early growth influences later BP. Cross-sectional studies at all ages of childhood and adulthood have shown associations of BP with both birth weight and rapid postnatal “catch-up” growth. Two “programming” hypotheses have emerged, with different emphases. One states that offspring BP is determined by maternal factors, which limit fetal growth. As a result, interventions to improve maternal nutrition and to increase infant caloric intake have been proposed. The other states that rapid postnatal growth in response to low birth weight is detrimental, so that infant caloric intake should be limited.

To address this controversy and establish the relative importance of height and adipose growth, we examined the influence of growth patterns on BP at age 10 years in a large, contemporary population of healthy children from the United Kingdom, recruited during gestation and followed up with serial measurements from birth.
Methods

Avon Longitudinal Study of Parents and Children Population

Avon Longitudinal Study of Parents and Children was established in 1990 to investigate the early life and genetic determinants of childhood health, development, and adult disease. The cohort and study design are detailed elsewhere (http://www.alspac.bris.ac.uk). Briefly, 14,541 pregnant women, expected to deliver between April 1990 and December 1992, were enrolled. A total of 14,062 live born children were followed up with questionnaires and, since the age of 7 years, at regular clinics until 2006 to establish anthropometric, behavioral, CV, and metabolic phenotypes. The Avon Longitudinal Study of Parents and Children Population

Anthropometric Measurements

Trained Avon Longitudinal Study of Parents and Children staff measured weight and crown-heel length (Harpenden Neonatometer; Holtain Ltd, Crymych, United Kingdom) at birth in 62% of subjects. Additional data were sourced from clinical records and birth notification. Weight and height were available from personal child health records until 5 years of age and have been shown to compare favorably with clinic measures from a subgroup. Subsequently, height and weight were measured during regular clinics with the children in light clothing, without shoes. Weight was measured to the nearest 100 g using Tanita scales (Wardworth Ltd, Bolton, United Kingdom). Height was measured to the nearest millimeter using a Harpenden stadiometer. Pubertal status was assessed by validated questionnaire.11

BP Measurement

At a median age of 10.6 years, children were asked to rest, without talking, for ≥5 minutes in the seated position before the first oscillometric BP measure was taken from the right arm using a Dinamap 9301 Vital Signs Monitor (Morton Medical, London, United Kingdom). The right arm was supported at midsternum level. Depending on arm circumference, 12- to 19-cm or 17- to 25-cm cuffs were used. The mean of 2 subsequent measures taken at 1-minute intervals was used. If 2 consecutive measures differed by >5 mm Hg, further measures were taken until stable readings were obtained.

Data Interpolation and Weight-for-Height Z Scores

Individual growth trajectories for height and weight, as a series of Z scores, were estimated for subjects with ≥2 temporally separated measures. Data >4 Z scores from the median were removed (24 weight estimates [0.03%] and 34 height estimates [0.04%]). For each individual growth trajectory, outliers were determined and removed after statistical comparison with the immediately preceding and following measures (912 weight estimates [1%] and 906 height estimates [1%]).

Weight and height measurements did not always coincide. To calculate weight-for-height Z scores, weight and height Z scores were interpolated linearly to an arbitrary, fixed-age scale. This was sampled on alternate days from birth to 3 months, then weekly until 1 year, and then every 2.4 months until 10 years. Weight and height

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Birth characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>3230</td>
<td>39.7 (1.3)</td>
<td>3346</td>
<td>39.8 (1.3)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3200</td>
<td>3.54 (0.49)</td>
<td>3301</td>
<td>3.43 (0.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Crown-heel length, cm</td>
<td>2581</td>
<td>51.3 (2.2)</td>
<td>2691</td>
<td>50.5 (2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>3230</td>
<td>10.6 (10.5–10.8)</td>
<td>3346</td>
<td>10.6 (10.5–10.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>3226</td>
<td>33.4 (29.9–38.2)</td>
<td>3345</td>
<td>34.0 (29.9–39.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>Height, cm</td>
<td>3222</td>
<td>140.4 (6.0)</td>
<td>3346</td>
<td>139.8 (6.2)</td>
<td>0.0005</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>3221</td>
<td>16.9 (15.7–18.8)</td>
<td>3345</td>
<td>17.4 (15.8–19.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>3230</td>
<td>104.0 (9.1)</td>
<td>3346</td>
<td>104.3 (9.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>3230</td>
<td>59.6 (7.9)</td>
<td>3346</td>
<td>60.9 (8.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parent-reported Tanner Stage†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1068</td>
<td>67.5%</td>
<td>592</td>
<td>33.2%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>434</td>
<td>27.4%</td>
<td>670</td>
<td>37.5%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>71</td>
<td>4.5%</td>
<td>385</td>
<td>21.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>0.4%</td>
<td>111</td>
<td>6.2%</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>0.1%</td>
<td>27</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Father, manual social class†</td>
<td>2839</td>
<td>50.1%</td>
<td>3007</td>
<td>52.1%</td>
<td>0.13</td>
</tr>
<tr>
<td>Mother, manual social class†</td>
<td>2683</td>
<td>58.2%</td>
<td>2800</td>
<td>58.1%</td>
<td>0.91</td>
</tr>
</tbody>
</table>

P values come from 2-way t test comparisons between the sexes. BP indicates blood pressure; BMI, body mass index. Values are median (interquartile range) and P values from Wilcoxon rank-sum tests. Values are percentages and P values from χ² tests.
at specific ages were estimated by back transformation of z scores to natural units. To assess adiposity trajectories, weight-for-height z scores were used in preference to body mass index (BMI; please see the online-only Data Supplement). Unlike BMI, this adiposity index is statistically independent of height at all ages and can, therefore, be used in multiple regression models to compare the relative strength of associations of height growth and fat accrual with outcomes.

### Conditional Growth Modeling

To assess growth over distinct age periods while eliminating some of the problems associated with highly correlated measures, we used conditional growth modeling (please see the online-only Data Supplement). For sequential growth intervals, variables were constructed that are statistically independent of each other, allowing inclusion together in multiple regression models. Thus, the influence of growth in specific intervals was assessed in comparison with, and adjusted for, growth in other intervals. We defined the intervals according to the correlation structure of the data so that they had approximately equal variability of growth. This resulted in sequential growth intervals between birth; 3.4 weeks; 1.9, 4.2, and 7.9 months; and 1.4, 3.2, 6.6, and 10 years for weight; between birth; 3.7 weeks; 2.0, 4.6, and 8.1 months; and 1.2, 2.2, 5.0, and 10.0 years for height; and between birth; 2.9 weeks; 1.6, 2.7, and 7.4 months; and 1.4, 3.2, 6.6, and 10.0 years for weight for height.

### Statistical Analysis

Further analyses were carried out using Stata 11 (StataCorp, College Station, TX). Cross-sectional analyses of the associations of height and weight-for-height with BP were carried out using multiple linear regression, adjusted for sex. Predictors in conditional growth models were initial measure of size, residualized growth variables for all periods up to the specified time point, and sex.

### Results

Table 1 describes the cohort. Birth weight and length were greater, and gestational age at birth was 0.09 weeks shorter in boys. Birth measures did not differ by source. Age, parental social class, and systolic BP did not differ by sex but boys were taller than girls, with lower weight, BMI, and diastolic BP at age 10 years. Pubertal status within 6 months of BP measurement was available for 51% of subjects, and although girls were more advanced than boys, only a small minority of boys (0.5%) and girls (7.7%) had advanced beyond Tanner Stage III.

At 10 years, 1 SD greater weight (7.1 kg in boys and 7.8 kg in girls) was associated with 1.93 mm Hg (95% CI,
1.72–2.15 mm Hg) greater systolic BP and 0.82 mm Hg (95% CI, 0.63–1.02 mm Hg) greater diastolic BP. In a multiple regression model, systolic BP was similarly associated with weight for height (1.50 mm Hg · SD\(^{-1}\) [95% CI, 1.27–1.72 mm Hg · SD\(^{-1}\)]) and height (1.22 mm Hg · SD\(^{-1}\) [95% CI, 1.00–1.44 mm Hg · SD\(^{-1}\)]) at 10 years, explaining 4.6% of its variance. Diastolic BP was associated with weight-for-height (1.13 mm Hg · SD\(^{-1}\) [95% CI, 0.93–1.33 mm Hg · SD\(^{-1}\)]) but not height (0.01 mm Hg · SD\(^{-1}\) [95% CI, −0.19 to 0.20 mm Hg · SD\(^{-1}\)]), explaining 2.5% of its variance. These associations did not differ by sex.

The independent associations of separate growth intervals with BP at 10 are shown in Figure 1. The values represent growth that is greater or less than normal population growth, analogous to the process of “crossing centiles” on growth charts. Using the graph of weight growth versus BP, as an example, highest BP at 10, would be expected for individuals with low birth weight, who cross centiles positively in all periods from birth to age 10 (birth to 3.4 weeks, 3.4 weeks to 1.9 months, etc). The similar modest positive associations with BP for the 5 periods ≤17 months suggest that “catch-up” growth effects are similar at any stage of infancy and less important than centile crossing after infancy.

Figure 1 suggests that a reasonable numeric summary of the results can be obtained using 3 key growth periods to evaluate the influences of growth before birth (prenatal), in the first 17 months of life (infancy), and between 17 months and 10 years (postinfancy growth; Table 2). As in the detailed models, the intervals were defined according to the correlation structure of the data. Although definitions of the term “infancy” vary, we have used it as a convenient description of the 17-month postnatal period defined by our simplified models. Greater systolic BP at 10 years was associated with lower prenatal growth of weight and weight for height but not height and with greater growth in any measure at any stage after birth. Greater diastolic BP at 10 years was associated with lower prenatal growth of weight and length but not weight for height and with postinfancy growth in weight and weight for height but not height. However, infancy growth in any measure had little effect on diastolic BP. In the postinfancy period, an SD change in weight had a greater effect on BP at 10 years than it did prenatally or in infancy.

To test the possibility that the associations of BP with prenatal and infant growth might be explained by a group of low birth weight subjects catching up on growth after birth, analyses were repeated excluding subjects with less than median birth weight. This gave similar results: 1-SD lower weight at birth was associated with 0.56-mm Hg higher systolic BP (\(P=0.028\)) and 0.49-mm Hg higher diastolic BP (\(P=0.031\)), and infancy weight gain was positively associated with later systolic BP (0.82 mm Hg · SD\(^{-1}\); \(P<0.001\)) but not diastolic BP (0.02 mm Hg · SD\(^{-1}\); \(P=0.9\)). Formal interaction testing showed no significant difference in the associations between growth in infancy and BP at 10 years, according to birth weight. Thus, the independent associations of reduced birth weight and of increased postnatal growth with raised BP at 10 are not confined to low birth weight subjects.

Average growth patterns in the 3 size parameters, according to categories of systolic and diastolic BPs, are shown in Figure 2. Children with higher systolic BP at age 10 years started life with, on average, lower weight, no difference in length, and no difference in weight for height from children with a lower BP. They steadily gained height, weight, and weight for height at a greater than average rate in their first 10 years, whereas those with lower BP grew at a lower rate than average. Most of the divergence in these parameters occurred after infancy, supporting the findings of the conditional growth models. All of the parameters showed a similar pattern, with weight having the strongest association. Patterns of associations of weight and weight for height with diastolic BP were very similar, although the effects were generally smaller, but associations of height with diastolic BP were markedly different. Children with higher diastolic BP at age 10 years started life shorter, whereas those with lower diastolic BP at age 10 years were longer, but there was little difference in height growth after this between children in the different diastolic BP groups.

### Table 2. Associations of Conditional Weight, Weight for Height, and Height Growth With BP at 10 Years for 3 Key Growth Periods (mm Hg · SD\(^{-1}\))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Systolic BP (95% CI)</th>
<th>P Value</th>
<th>Diastolic BP (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prenatal growth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>−0.33 (−0.55 to −0.11)</td>
<td>0.003</td>
<td>−0.28 (−0.47 to −0.08)</td>
<td>0.006</td>
</tr>
<tr>
<td>Weight for height</td>
<td>−0.27 (−0.52 to −0.02)</td>
<td>0.035</td>
<td>−0.12 (−0.35 to 0.10)</td>
<td>0.27</td>
</tr>
<tr>
<td>Height</td>
<td>−0.12 (−0.37 to 0.13)</td>
<td>0.35</td>
<td>−0.27 (−0.49 to −0.05)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Infant growth (0–17 mo)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.90 (0.68–1.12)</td>
<td>&lt;0.001</td>
<td>0.18 (−0.02 to 0.37)</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight for height</td>
<td>0.41 (0.16–0.66)</td>
<td>&lt;0.001</td>
<td>0.06 (−0.16 to 0.28)</td>
<td>0.57</td>
</tr>
<tr>
<td>Height</td>
<td>0.82 (0.56–1.07)</td>
<td>&lt;0.001</td>
<td>0.08 (−0.14 to 0.30)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Postinfancy growth (&gt;17 mo to 10 y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>1.91 (1.69–2.13)</td>
<td>&lt;0.001</td>
<td>0.95 (0.76–1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight for height</td>
<td>1.56 (1.32–1.81)</td>
<td>&lt;0.001</td>
<td>1.14 (0.92–1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height</td>
<td>1.20 (0.96–1.45)</td>
<td>&lt;0.001</td>
<td>0.22 (−0.002 to 0.43)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

All models were adjusted for sex. BP indicates blood pressure.
In the largest reported contemporary cohort of healthy, prepubertal children, we found that the strongest anthropometric association with BP at 10 years was weight gain after infancy, with contributions from both height and weight for height (a marker of adiposity). There were effects of size at birth and of early postnatal growth, as reported previously, but their magnitude was substantially smaller. Because BP at age 10 years is related substantially to adult BP, our findings support public health policy to reduce adiposity in children.

There is increasing interest in the effects of early life on future CV risk. Considerable emphasis has been put on prenatal and early postnatal influences. These were confirmed in our study but found to be independent of each other and relatively small. Our findings support previous associations between catch-up growth in low birth weight individuals and later BP. However, the influence of early postnatal growth did not depend solely on a subpopulation catching up from low weight, because similar associations were found when subjects with less than median birth weight were excluded.

Growth after infancy was more strongly associated with later BP than growth in infancy or prenatal growth, supporting evidence that growth in early life has less influence on adult BP than growth in later childhood. This is consistent with evidence that growth after 11 years has a greater effect on adult BP than previous growth and with recent findings from this cohort that later adiposity increments have a greater association with BP at 16 years than earlier ones. It is interesting that height and adipose growth had almost equal associations with systolic BP. This suggests that, in postnatal life, acquisition of mass, regardless of tissue type, increases systolic BP. However, this was not the case for diastolic BP, which was only associated with postinfancy growth. Lowest BP was associated, not with average growth, but with growth that was lower than predicted by early size. This supports the concept that mismatch between early life specification of systems and eventual demands placed on them may determine BP status. Animal data suggest that demands on renal capacity made by rapid childhood growth may not be met completely by renal development, resulting in
compensatory BP increases. Other systems may also be affected. Although nephron numbers are largely determined by birth, so too are cardiac myocyte populations, arteriolar wall structures, and vessel densities.17

Our data, at first sight, might suggest that limiting growth after birth in any form should be beneficial. Although this might lower BP, negative consequences are likely. For example, final height is inversely related to coronary heart disease risk.18 Thus, strategies to reduce adiposity alone are more likely to be beneficial, given known associations between obesity and CV risk.5,19

Body mass explained ≈5% of systolic BP variance at age 10 years. However, we have not fully accounted for the considerable momentary and daily BP variability in individuals or the ±5% to 10% error of BP devices. Thus, we may have underestimated the true association of growth with long-term BP status. Although other factors undoubtedly influence BP, meaningful reductions in CV risk could be achieved by BP reductions resulting from decreased adiposity.5,19

BP in childhood is less likely to be influenced by the effects of aging and chronic disease on the CV system. Thus, effects of growth should be more apparent. We chose to study BP at age 10 years to minimize the effects of puberty on BP. Although our questionnaire assessment of pubertal status was limited, it was sufficient to determine that the majority of subjects had not achieved advanced puberty. Deviations from average growth in this cohort were assessed using relevant data from the same population rather than a reference population. Many longitudinal growth studies have examined the stages of childhood growth using only a few divisions of the age range. In contrast, we chose intervals defined by the correlation structure of our data so that each had an approximately equal change in rank ordering of individuals for a given measure. This yielded periods of differing chronological time but of arguably similar biological importance. The amount of data available in our study, particularly in early life, enabled unusually short periods of growth to be studied while maintaining good levels of precision. This allowed for a detailed assessment of the influence of different growth periods on later BP. It also enabled a simpler model, limited to 3 growth periods of prenatal life, infancy, and postinfancy to be constructed. Unfortunately, the timing and influence of adiposity rebound could not be examined because of sparse data at age 6 years.

We used weight-for-height z score to assess adiposity. Unlike BMI or ponderal index, this measure removes the age-varying correlation between height and weight entirely and therefore allows for meaningful comparisons between age groups and estimation of relative contributions of height versus adipose growth. In common with other indices, this measure estimates adiposity indirectly and may, therefore, be influenced by changes in lean mass that are not related to height growth. Direct measures using technologies such as dual-energy x-ray absorptiometry are possible but not practical in studies like ours. However, such measures would be necessary to estimate the portion of overall mass attributed to the expected increase in bone mineral density that results from increased adiposity.20 We showed recently in this cohort that weight-for-height indices such as BMI are comparable to x-ray absorptiometry fat mass in their associations with CV risk factors.5,19

Perspectives
Raised BP is associated with more global mortality than any other risk factor. Many adults require lifelong treatment, often with multiple drugs, to achieve target BP levels. Nevertheless, their risk remains much higher than for people with the same BP who were never hypertensive.21 Furthermore, such therapies do little to alter the risk profile of the whole population, where the number of deaths from BP-related conditions exceeds that for the hypertensive subpopulation.22 Because BP ranking relative to the population is substantially determined in the first decade of life,3 BP reduction strategies aimed at children should have lifelong benefit in terms of CV risk. Our study suggests that a focus on strategies to reduce the development of adiposity from infancy onward, rather than an emphasis on the nutrition and weight of mothers and infants, should bring greater reductions in population BP.

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We thank the families, midwives, the team from the Avon Longitudinal Study of Parents and Children, Dr Vivek Muthurangu, and Prof Clive Osmond for help with the article.

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Disclosures
None.

References
gestational age: is there an adverse effect on later blood pressure? Circulation. 2007;115:213–220.


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ADIPOSE AND HEIGHT GROWTH THROUGH CHILDHOOD AND BLOOD PRESSURE STATUS IN A LARGE PROSPECTIVE COHORT STUDY

ONLINE SUPPLEMENT

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SUPPLEMENTAL METHODS

Growth Curve Modelling

For each sex, age-varying location (median), scale (coefficient of variation) and shape (skewness and kurtosis) of the underlying distributions of height and weight were modelled by fitting Box-Cox distributions. Age-varying functions for the four distribution parameters were fitted using smoothing cubic splines. To ensure a good fit with these splines and given the relatively complex shape of growth curves in infancy compared to later ages, a power transform of age was used to expand the age scale in infancy and compress it in later childhood. The optimum power transform and the optimum number of degrees of freedom for each cubic spline model were found using an optimization procedure with the Bayesian information criterion as a penalty function. An adequate goodness-of-fit for the growth curve models was confirmed using Q tests and worm plots (not presented). Figure S1 shows the fit of these models to the data. Weight growth curves were fitted using 91,299 measures in boys and 89,603 measures in girls. For height, these values were 49,641 and 48,194, respectively. The median number of measures used to construct individual growth trajectories was 13 (IQR 7–20) for weight and 7 (IQR 4–10) for height.

Weight-for-height z-Score

To assess adiposity trajectories, weight-for-height z-scores were calculated from the weight and height z-scores, in preference to using BMI:

\[ z(\text{weight} - \text{for height}) = \frac{z(\text{weight}) - r \cdot z(\text{height})}{\sqrt{1 - r^2}} \]

where \( r \) is the age- and sex-specific correlation between weight and height. These allow a more meaningful comparison to be made between assessments of adiposity at different ages because, in contrast to BMI, account is taken of the varying relationship between weight and height through childhood. Furthermore, by construction, weight-for-height z-score, unlike BMI, is uncorrelated with height z-score at all ages. This allows regression models containing both measures to assess the relative strength of associations of height and adiposity with a given outcome. Thus, the influences of skeletal growth (the dominant factor in changes in height) and of accrual of fat might be differentiated.

BMI and ponderal index (weight divided by height cubed) z-scores were also calculated for comparison with weight-for-height z-scores. Change in BMI and ponderal index z-scores for each growth period had similar associations with blood pressure to those of weight-for-height z-score (not shown). However, associations were weaker and more variable during infancy for BMI and during later childhood for ponderal index. These indices were originally designed to adjust weight for variations in height so that variation in adiposity, the principal determinant of weight variability for a given height, might be determined. However, correlations of BMI with height increase with decreasing age in childhood and correlations of ponderal index increase...
with increasing age. Thus, neither represents an adequate adjustment of weight for height throughout childhood. By contrast, weight-for-height z-score has zero correlation with height at all ages and is, therefore, optimal for this task.

**Conditional Growth Modelling**

Conditional growth modelling uses the standardised residuals from multiple linear regression analysis of the degree to which a size measure at a later age differs from that predicted by all prior growth measures plus the initial measure of size. Such measures are entirely uncorrelated with each other (statistically independent) and, when included in a multiple regression model with all prior growth measures upon which they are conditioned, allow the independent influences of growth over discrete intervals to be estimated. It has been pointed out that conditional growth model equations can be rewritten as traditional multiple regression models that include correlated growth measures. Thus, the advantages of conditional growth modelling have been questioned. However, two important advantages over prior approaches have been identified: They remove the often strong correlation between different growth measures allowing large numbers of parameters to be included in a single, fully adjusted model of growth and they facilitate interpretation of the results where previous approaches, it has been argued, may lead to misunderstandings of the importance of specific periods of growth.

The number and choice of intervals is important. Fewer intervals will increase the estimate accuracy for the overall influence of growth over the periods considered, but may fail to reveal important biological differences in the influences of growth during different stages of development. Increasing the number of intervals sacrifices accuracy of the estimates for greater temporal resolution of the influences of growth at different ages. For a given growth parameter, the accuracy of the estimate over an interval depends on the number of individuals whose rank ordering in the population changed in that time. In large datasets, this occurs sufficiently over relatively short intervals to allow accurate estimation with greater temporal resolution. In our analysis, we chose to divide growth between birth and 10 years of age into eight intervals. Interval length was determined using the correlation structure of the data so that an approximately equal change in the rank ordering of individuals occurred in each. This yields periods of differing chronological time but of arguably similar biological meaning and associations of growth in these intervals with outcome measures should have similar accuracy.

**Supplemental References**

Figure S1. Growth curves fitted to 49,614 measures of height in boys and 48,194 measures of height in girls and to 91,299 measures of weight in boys and 89,603 measures of weight in girls between birth and age ten years. Sparse data between ages five and seven years separates early data drawn from personal health records and later data measured during clinics. The timing of these clinics and, to a lesser extent timing of routine community measures before five years, can be seen as clusters of data. Centile lines, separated by two thirds of a standard deviation, are shown. Inset figures show the good fit of the models to early postnatal changes in weight.