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 *t* distributions.[1] 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.[2] An adequate goodness-of-fit for the growth curve models was confirmed using Q tests[3] and worm plots[4] (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:

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

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.[5] 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[6] that include correlated growth measures.[7] 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.[7, 8]

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

1. Rigby RA, Stasinopoulos DM. Using the Box-Cox t distribution in GAMLSS to model skewness and kurtosis. *Statistical Modelling*. 2006;6:209-229.
2. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS) in R. *J Stat Softw*. 2007;23.
3. Royston P, Wright EM. Goodness-of-fit statistics for age-specific reference intervals. *Stat Med*. 2000;19:2943-2962.
4. van Buuren S, Fredriks M. Worm plot: a simple diagnostic device for modelling growth reference curves. *Stat Med*. 2001;20:1259-1277.

5. Cole TJ. A new index of child weight-for-height based on weight and height Z scores. *Ann Hum Biol*. 1994;21:96.
6. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease - the hypothesis revisited. *BMJ*. 1999;319:245-249.
7. Tu YK, Gilthorpe MS. Unexplained residuals models are not solutions to statistical modeling of the fetal origins hypothesis. *J Clin Epidemiol*. 2007;60:318-319; author reply 319-320.
8. Keijzer-Veen MG, Euser AM, van Montfoort N, Dekker FW, Vandenbroucke JP, Van Houwelingen HC. A regression model with unexplained residuals was preferred in the analysis of the fetal origins of adult diseases hypothesis. *J Clin Epidemiol*. 2005;58:1320-1324.

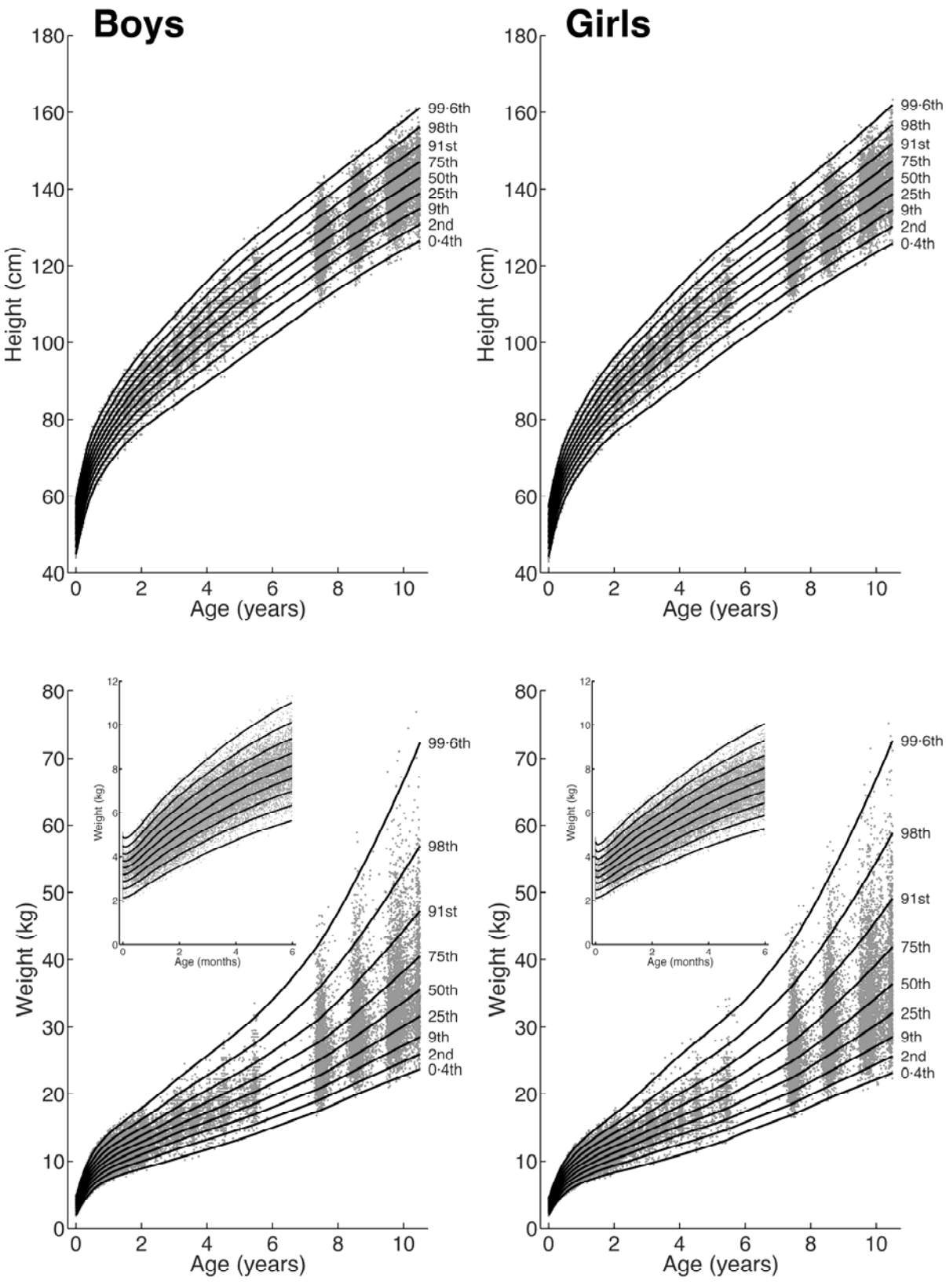
Boys
Girls
Height (cm)
Age (years)
Weight (kg)
Age (months)
99·6th
98th
91st
75th
50th
25th
9th
2nd
0·4th

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.