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Analysis of "Sensitive" Periods of Fetal and Child Growth

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ABSTRACT

Background: Birth weight and weight gain in infancy and early childhood are commonly studied as risk factors for later cardiometabolic diseases. In this study, we explore methods for quantifying weight gain during different age periods and for comparing the magnitude of the associations with later blood pressure.

Methods: Based on data from a birth cohort study nested within a large cluster-randomized trial with repeated measures of weight from birth to 16 years of age, we compared the results of four analytic approaches to assess sensitive periods of growth on blood pressure at age 16 years.

Results: Approaches based on z-scores of weight or weight gain velocity (both standardized for age and sex), or on regression-based conditional weight standardized residuals, yielded more coherent results than an approach based on absolute weight gain velocity. Weight gain standardized by sex and age was positively associated with blood pressure at 16 years at all postnatal age periods, but the magnitude of association was larger during adolescence (11.5 to 16 years) than during earlier intervals (0-3 months, 3-12 months, 1-6.5 years, or 6.5-11.5 years).

Conclusions: Standardization of weight and weight gain by age and sex, or regression-based standardized residuals based on conditional weight, reflects relative gain and thus accounts for the rapid weight gains normally observed in early infancy and puberty. Adolescence appears to be a more sensitive period for relative weight gain effects on later blood pressure than earlier periods, even those of similar duration.

Word count: 241

Key words: growth; weight gain; blood pressure; developmental origins of health and disease

KEY MESSAGES

- Methods for quantifying weight gain often ignore the normal deceleration in growth that occurs in infancy and early childhood and the later acceleration at puberty, and the periods compared are often of unequal duration.

- Relative weight gain (z-scores standardized for age and sex) and regression-based conditional weight standardized residuals adequately account for changes in growth rates with age but not for unequal time periods.

- Modeling of relative weight gain and comparing periods of similar duration reveal a pattern of increasing magnitude of association with advancing age in relation to blood pressure at 16 years.

INTRODUCTION

One of the major tenets of the developmental origins of health and disease (DOHaD) hypothesis is that exposure to nutritional, socioeconomic, and other environmental agents or processes has a major effect on later chronic disease risk when it occurs during "critical" or "sensitive" early developmental periods, i.e., pre-conception, pregnancy, infancy, and childhood. A critical age period can be defined as one in which an exposure must occur to influence a later outcome, while a sensitive period is one in which an exposure has a larger effect than the same exposure during other periods.(1, 2)

Growth is probably the most common exposure studied with respect to adult chronic cardiometabolic diseases. Knowing whether insufficient or excessive growth during critical or sensitive periods is associated with later cardiometabolic diseases presents unique methodologic challenges.(1, 3-6) By definition, growth is increase in size over time. But issues such as absolute vs relative increase, duration of time over which the growth is measured, and time of life (age) affect the analytic approach used and the inferences drawn therefrom. It is well known that the rate of weight gain (the most common measure of growth) decreases with age, at least until puberty. Moreover, the age periods postulated to be critical or sensitive are of different durations, which often reflect practical issues such as the difficulty in estimating fetal weight and acceptable frequencies and ages of measurement.

We have used data from a birth cohort nested within a large cluster-randomized trial,(7) with repeated anthropometric measures obtained during infancy, childhood, and adolescence, to

compare different analytic approaches to quantifying the association between growth during these periods and blood pressure at 16 years of age. The age periods compared are pregnancy (denoted by weight at birth standardized for gestational age and sex), birth to 3 months, 3 to 12 months, 12 months to 6.5 years, 6.5 to 11.5 years, and 11.5 to 16 years. We show that inferences about the "sensitivity" of growth periods depend on how growth is quantified. Our results should therefore be of interest for lifecourse epidemiology in general, and DOHaD in particular.

METHODS

Study sample

Our study is based on an observational analysis of data collected in the Promotion of Breastfeeding Intervention Trial (PROBIT), a multi-centre, clustered-randomized trial conducted in the Republic of Belarus.(7) The clusters were maternity hospitals and one affiliated polyclinic (outpatient clinic). A total of 17,046 healthy, singleton, breastfed newborns (≥37 completed weeks of gestation, ≥2.5 kg birth weight, and 5-minute Apgar scores ≥5) and their mothers were recruited from 31 maternity hospitals between June 1996 and December 1997. The infants were followed up by their polyclinic pediatricians at 1, 2, 3, 6, 9, and 12 months, when infant weight and length were measured. (7)

Follow-up interviews and examinations, which included measurements of length/height, weight, skinfold thicknesses, and blood pressure were subsequently carried out at mean ages of 6.5, 11.5, and 16 years: 13,889 children (81.5% of the original cohort) attended the follow-up visit at 6.5 years,(8) 13,879 (81.4% of the original cohort) at 11.5 years,(9) and 13,557 (79.5% of the

original cohort) at 16 years.(10) At 6.5, 11.5, and 16 years, all anthropometric outcomes were measured at dedicated research clinics using uniform research-specific equipment, with standardized training and quality assurance procedures (8-10). Following completion of the initial visits, audit visits on a randomly selected subsample were conducted to ensure interobserver reproducibility. Weight was measured on an electronic digital scale (Seca Bella 840 for 6.5-year follow-up visit; Tanita TBF 300GS body fat analyzer for 11.5- and 16-year follow-up visits), obtained in duplicate, and averaged. (8-10) At 16 years, systolic and diastolic blood pressures were measured in duplicate using a digital oscillometric device (705IT; Omron Healthcare).(10) No data were collected on diet or physical activity. A total of 12,072 children (70.8%) attended all three follow-up visits at 6.5, 11.5, and 16 years. We excluded 136 children with missing data on weight in the first year (birth, 3 months, and 12 months) (93), 6.5 years (6), 11.5 years (7), or 16 years (19); or on blood pressure at 16 years (24). Our study sample for this analysis of data from birth to adolescence therefore comprises 11,936 children, 70.0% of the original birth cohort; no values were imputed for those excluded.

The initial PROBIT trial and all subsequent follow-ups were approved by the Belarussian 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 (ALSPAC) 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-year and 16-year visits.

Quantifying childhood weight gain

We explore how different approaches to analyzing childhood weight gain can affect estimates of associations with later systolic and diastolic blood pressure and the inferences that derive from those estimates. We focus on weight gain during six age periods with potential etiological relevance to blood pressure in late adolescence: pregnancy, birth to 3 months, 3 to 12 months, 12 months to 6.5 years, 6.5 to 11.5 years, and 11.5 to 16 years. These postnatal age periods are not arbitrary; the first three derive from a cubic spline-based analysis of the PROBIT cohort demonstrating knots at 3 and 12 months, with linear changes in weight gain between successive knots (11); the latter two periods correspond to our subsequently funded follow-up visits.

We used four different analytic approaches. The first is based on weight gain velocity during each period, calculated as total weight gain divided by length of the time interval:

$$x_{1,j} = \frac{\left(W_j - W_{j-1}\right)}{d_j},$$

where *j* indexes the age at study, W_j is weight at age j, and d_j is the difference (in months) between time *j* and time *j-1*. For example, if *j* is the 12-month time point and *j-1* is the 3-month time point, then W_j and W_{j-1} are the weights at 12 and 3 months, respectively, and d_j is 12 – 3 = 9 months.

The second analytic approach uses change in age- and sex-specific weight-for-age z-scores for each child during each period:

$$z_{2,j} = \frac{\left(W_j - \bar{W}_j\right)}{SD(W_j)},$$

where $\bar{W}_j$ is the mean weight for sex and age j at study and $SD(W_j)$ is the corresponding standard deviation.

The values compared in the second approach are then the difference in z-scores at the two ages defining the period:

$$x_{2,j} = \ z_{2,j} - z_{2,j-1}$$

The third approach is based on age- and sex-specific weight gain velocity z-scores,

$$x_{3,j} = \frac{\left(x_{1,j} - \bar{x}_{1,j}\right)}{SD(x_{1,j})}.$$

where $x_{1,j}$ is the weight gain velocity between *j-1* and *j* (as defined in the first approach), $\bar{x}_{1,j}$ is the mean sex-specific weight gain velocity during the period, and $SD(x_{1,j})$ is the corresponding standard deviation.

The second and third approaches are based on an internal (PROBIT) standard, i.e., sex- and age-specific means and standard deviations for weight and weight gain velocity, respectively, estimated from the PROBIT sample. At birth, sex-specific birth weight-for-gestational-age z-scores are also based on this internal standard. In the follow-up visits at 6.5, 11.5, and 16 years, children's weights were not collected at exactly 78, 138, and 192 months. Weights at 78, 138, and 192 months were extrapolated from weights at the 12-month, 6.5-year, 11.5-year, and 16-year follow-up visits. For example, weight at 78 months (6.5 years) was linearly extrapolated from the weights measured at the 12-month and 6.5-year follow-up visits. Weights at 138 months (11.5 years) and 192 months (16 years) were estimated similarly. These extrapolated weights

were then used (in the second approach) to construct sex-specific weight-for-age z-scores at 78, 138, and 192 months.

The fourth approach is based on age- and sex-specific conditional weight standardized residuals (12, 13):

$$x_{4,j} = \frac{\left(W_j - \widehat{W_j}\right)}{SDRj},$$

where W_j *is* the observed weight at age j, $\widehat{W_j}$ is the predicted weight at age j estimated from a sex-stratified linear regression of weight at age j on all prior weights, SDR_j is the standard deviation of the residual $\left(W_j - \widehat{W_j}\right)$, as estimated from the regression model. The regression model also includes quadratic terms for prior weights to account for non-linearity.(12) The conditional weight residual at age j, ($W_j - \widehat{W_j}$), is the deviation in a child's weight from the child's expected weight (i.e., the difference between the observed and expected weight gains over the interval, given all prior weights). These conditional weight standardized residuals at 3, 12, 78, 138, and 172 months are independent of one another.(12)

Statistical analysis

For all four approaches, our analysis is based on linear regression models to assess the association between child growth (exposure) during the studied age periods and both systolic and diastolic blood pressure (outcomes) at age 16 years. All models account for clustering within polyclinics by including a random effect term for polyclinic. In the first three approaches, for each model and each age period, we compare the results after adjustment for sex (weight z-scores and weight gain velocity z-scores are already standardized by sex) and growth in all preceding age periods (including at birth), but not in subsequent age periods.(5, 6, 11, 12) In the

fourth approach, however, we include conditional weights for all age periods in a single regression model, since each conditional weight is uncorrelated with earlier or later conditional weights.

We also compare the results of the same models after adjustment for other baseline covariates, including maternal age, maternal and paternal height and BMI, maternal education, and geographic region. Maternal age is categorized as <20 years, 20-34 years, and ≥35 years; maternal and paternal height and were reported by the mother at the 6.5-year follow-up visit and serve as proxies for those variables at birth. Maternal education (reported at recruitment) is categorized as "university," "partial university," "high school," or "incomplete high school." Geographic region is defined by four categories based on East vs West geographic region, and urban vs rural residence. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 summarizes the baseline characteristics of the 11,936 PROBIT children with complete data through 16 years. The median ages (and interquartile ranges) at the three long-term follow-up examinations were 6.5 years (±1 month), 11.6 years (±3 months), and 16.1 years (±3 months). Mean weights for participating children at birth, 3 months, 12 months, 78 months (6.5 years), 138 months (11.5 years), and 192 months (16 years) are shown in Table 2, along with the weight gain velocity during the corresponding intervals. As expected, infants grew fastest in the first 3 months after birth, nearly 0.89 kg per month, and at half that rate from 3 to 12 months (0.50 kg

per month). From 12 months to 6.5 years of age, weight gain decreased to 0.18 kg per month, then nearly doubled to 0.31 kg per month from 6.5 to 11.5 years of age, and increased further to 0.39 kg per month from 11.5 to 16 years of age.

The results of the regression models for each studied age period for systolic and diastolic blood pressure and absolute weight gain velocity, sex-specific weight-for-age z-scores, weight gain velocity z-scores, and conditional weight standardized residuals are presented in Table 3, with and without adjustment for other baseline covariates. The results from the fully-adjusted models were similar to those of the partially-adjusted models. As shown in Table 3a, the fully-adjusted changes in systolic blood pressure per kg/month increase in absolute weight gain velocity (first approach) varied widely. The strongest association with systolic blood pressure at 16 years (45.6 mm Hg increase per kg/mo) was observed for the period 12 months to 6.5 years, when weight gain was slowest at 0.18 kg/month, while the weakest association (3.0 mm Hg increase per kg/mo) occurred in the first 3 months, when weight gain was fastest at 0.89 kg/month. With standardization of growth measures for age and sex in the second, third, and fourth analytic approaches, estimated increases in systolic blood pressures rose progressively from 0.6, 0.5, 0.6 mg Hg per SD increase, respectively, in the first 3 months after birth to 4.2, 3.1, and 2.8 mm Hg per SD increase in the oldest observed period (11.5 to 16 years of age). Estimated changes in diastolic blood pressure showed a similar pattern (Table 3b).

DISCUSSION

In the DOHaD literature, growth in weight, length/height, and body mass index (BMI) have often been studied at birth and during infancy and childhood for their associations with adiposity, obesity, blood pressure, and other cardiometabolic outcomes later in life.(6, 12-16) One of the key DOHaD hypotheses has been the existence of sensitive periods during pregnancy and early infancy, during which insufficient or excessive growth is postulated to have a larger effect on these later outcomes than does growth during later periods. As we (17, 18) and others (19) have pointed out, however, much of the evidence supporting the "effects" of restricted fetal growth has been based on the inappropriate over-adjustment for size at follow-up, a mediator of later cardiometabolic outcomes.

Most previous investigators have quantified growth by subtracting anthropometric measurements made at two time points, without even dividing by (or adjusting for) the time interval between them.(20) Two additional issues complicate the quantification of growth during childhood. First, growth is most rapid during fetal life and shortly after birth, decelerating thereafter until the pubertal growth spurt, following which growth again slows until attainment of final adult height. Thus, comparisons of absolute weight, length, or BMI gains at different periods of life will be affected by these underlying differences in growth rates at different ages and may promote misleading inferences about their relative importance for later outcomes. Second, the periods compared are of unequal duration. Pregnancy typically lasts 9 months, "early infancy" 3-6 months, "late infancy" 6-9 months, and "early childhood" anywhere from 1 to 10 years. Comparisons of associations with growth during these periods should ideally also account for

their unequal durations, but monthly (or even 3-monthly) measurements throughout pregnancy, infancy, childhood, and adolescence are burdensome and costly.

In this paper, we compare four analytic approaches for quantifying the effects of weight gain during childhood on later blood pressure. The first approach, based on absolute weight gain velocity, averages the absolute weight gain over the length of the period but does not account for the unequal durations of the periods examined, nor for the deceleration in weight gain with advancing age (until puberty) and acceleration thereafter. The second approach, based on change in weight z-score, accounts for the different rates of weight gain at different ages, but shares the same shortcoming of unequal time intervals. The third approach, based on z-scores for weight gain velocity, yields similar results to the second approach; it also accounts for the different rates of weight gain at different ages, but not for the unequal time intervals. The fourth approach, based on conditional weight standardized residuals, also yields similar results and accounts for different rates of weight gain at different ages, but with slightly smaller magnitudes of association and narrower confidence intervals in the last two age intervals.

As shown in Table 3, the four approaches we compare lead to different inferences concerning the "sensitivity" of the five postnatal age periods compared (0-3 months, 3-12 months, 1-6.5 years, 6.5-11.5 years, and 11.5-16 years) with respect to systolic and diastolic blood pressure at 16 years of age. The second (comparison of change in weight-for-age z-scores), third (based on z-scores for weight gain velocity), and fourth (based on conditional weight standardized residuals) analytic approaches yielded very similar results for all periods; all three of these approaches showed a pattern of increasing magnitudes of association with advancing age. This is contrast to

the inverted U-shaped pattern observed with the first approach. The non-significant inverse association we observed with birth weight z-score [-0.02 (95% CI -0.23 to +0.18) mm Hg systolic blood pressure per SD increase] is consistent in direction with that postulated by the DOHaD hypothesis. For all postnatal periods, however, increased growth was associated with higher blood pressure at 16 years. The magnitudes of these postnatal associations are not directly comparable, however, because of the shorter duration of the infant age periods (0-3 and 3-12 months) vs those during later childhood (which varied from 4.5 to 5.5 years).

The second analytic approach models the change in z-scores for weight, while the third approach models the z-score for change in weight. The fourth approach models the conditional weight, which can be interpreted as the difference in the observed weight from the expected weight over an interval according to weight over all prior intervals. Units of weight change in these three approaches are not identical, and thus their magnitudes of association cannot be directly compared. The associations show the same relative magnitudes and temporal pattern, however, across the age periods compared. In the second and third approaches, weight gain is calculated directly based on weights at the two ages defining each age interval. Because weight change in any period is not independent of weight gains in previous periods, the magnitude of association for weight gain during that period may therefore be inflated or deflated in these two approaches.

In the fourth approach, the conditional weight for each period is estimated from a regression model based on ***all*** previous and subsequent weights; conditional weight standardized residuals at all ages periods are thus independent of one another. One advantage of the fourth approach is that we can include all standardized uncorrelated conditional weights from all age periods in a

single model, instead of the series of sequential models as in the second and the third approaches. Nonetheless, the conditional weight residuals are calculated based on a series of sequential models. All three of approaches 2-4 show larger associations of later blood pressure with weight gain during adolescence (11.5 to 16 years) than during intervals of slightly longer duration earlier in childhood (1-6.5 years and 6.5-11.5 years). These results are qualitatively similar to those recently reported from the Project Viva cohort (Boston)(21) and the GUSTO cohort (Singapore)(22), based on outcomes measured in early and mid-childhood.

The first analytic approach (based on absolute weight gain velocities over each period) shows the largest apparent "sensitivity" (magnitude of association between weight gain and later blood pressure) during the 1-6.5 year period, when weight gain velocity was lowest. It also shows lower apparent sensitivity during later periods when weight gain increases again at puberty. Moreover, the apparent "effects" of weight gain in all post-infancy periods appear very large with the first approach (Table 3), because they are based on rates of absolute weight gain (in kg per month) that are common during early infancy but virtually never observed at later ages (Table 2). For these reasons, the associations obtained from the first method require care when comparing time periods characterized by different absolute growth rates.

We emphasize, however, that the first analytic approach is not "wrong" in any absolute sense. Providing that investigators adjust for growth in temporally precedent age periods and do not over-adjust for temporally distal mediators or proxies, analyzing effects of weight gain expressed in kg/month can yield valid associations on the kg/month scale. From a counterfactual perspective, it is theoretically possible to intervene (by force-feeding) from birth to 3 months to

induce a 1 kg/month gain in weight from birth to 3 months and compare later outcomes with those observed after force-feeding to induce the same 1 kg/month weight gain during a 3-month period in adolescence. Of course, both interventions are infeasible and unethical in human children. It is precisely because of these problems, however, that observational results based on metrics of absolute weight gain are misleading. In contrast, results based on relative weight gains (the second, third, and fourth approaches) lead to straightforward interpretations from feasible, ethical counterfactual interventions.(23)Strengths of our study include its large sample size, high rate of follow-up, frequent measures of weight at birth and throughout infancy, standardized oscillometric assessment of blood pressure, and measurement of many potential confounding factors. One potential weakness is that growth differences in infancy were not major hypotheses of the original PROBIT trial, which focused on risks of infection and atopic eczema during the first 12 months of life.(7) Unlike the weights obtained at 6.5, 11.5, and 16 years, weights obtained during infancy were not standardized with respect to weighing scales and measurement methods across the 31 participating polyclinics. That lack of standardization should have led to non-differential measurement error, however, and therefore should not affect the comparison of the three analytic approaches we report on in this paper. Both diet and physical activity are known to influence both weight gain in childhood and blood pressure in adulthood. We collected no data on these variables, however, and thus cannot assess their independent contributions to later blood pressure, nor control for their potential to confound the observed associations with weight gain. Finally, all four of our analytic approaches assume no residual confounding, i.e., that confounders are invariable over time and are adequately measured and adjusted for.

Our findings would benefit from replication in other cohorts. If confirmed, they have important implications for investigators exploring the biological mechanisms underlying the increase with age in magnitude of association between weight gain and later adverse cardiometabolic outcomes, as well as those seeking to develop and test preventive interventions.

Word count: 3,514

Table 1. Baseline characteristics of PROBIT children who attended all of the follow-up visits at 6.5, 11.5 years, and 16 years of age (n=11,936)

Characteristic	
Place or residence, N (%)	
East/urban	3,696 (31.0)
East/rural	1,941 (16.3)
West/urban	2,787 (23.4)
West/rural	3,512 (29.4)
Maternal age, N (%)	
< 20 years	1,581 (13.3)
20-34 years	9,872 (82.7)
≥35 years	483 (4.1)
Maternal education, N (%)	
Completed university	1,591 (13.3)
Partial university	6,179 (51.7)
Completed secondary school	3,766 (31.6)
Incomplete secondary school	400 (3.4)
Maternal height (cm), mean ± SD*	164.4 ± 5.7
Maternal BMI (kg/m^2), mean ± SD*	24.5 ± 4.4
Paternal height (cm), mean ± SD*	176.1 ± 6.7
Paternal BMI (kg/m^2), mean ± SD*	25.7 ± 3.3

* Based on heights and weights reported by the mother at the 6.5-year visit

Table 2. Weight, weight gain, and weight gain velocity (mean ± SD)

Age	Weight (kg)	Weight gain (kg)	Weight gain velocity (kg/mo)
Birth	3.4 ± 0.4	--	--
3 months	6.1 ± 0.7	2.7 ± 0.7	0.89 ± 0.19
12 months	10.6 ± 1.0	4.5 ± 0.9	0.50 ± 0.10
78 months**	22.5 ± 3.5	12.0 ± 3.2	0.18 ± 0.05
138 months**	40.7 ± 9.0	18.3 ± 7.0	0.31 ± 0.12
192 months**	61.7 ± 11.9	21.0 ± 9.3	0.39 ± 0.17

** Weights at 78, 138, and 192 months were linearly extrapolated, based on weights at the 12-month and 6.5-year, 11.5-year, and 16-year follow-up examinations, respectively.

Table 3. Parameter estimates (95% confidence intervals) from regression models and partial correlation coefficients

a. Systolic blood pressure

Analytic Approach	Partially-Adjusted Model*	Fully-Adjusted Model**
Absolute weight gain velocity (kg/mo)		
0-3 months	2.9 (1.9-4.0)	3.0 (1.9-4.1)
3-12 months	9.4 (7.4-11.5)	8.3 (6.2-10.4)
1-6.5 years	48.1 (44.1-52.0)	45.6 (41.3-50.0)
6.5-11.5 years	16.4 (14.6-18.1)	15.5 (13.7-17.4)
11.5-16 years	19.8 (18.6-21.0)	19.6 (18.3-20.9)
Change in sex-specific weight-for-age z-score		
0-3 months	0.59 (0.38-0.82)	0.58 (0.35-0.81)
3-12 months	1.03 (0.81-1.25)	0.90 (0.67-1.13)
1-6.5 years	2.56 (2.35-2.77)	2.44 (2.21-2.67)
6.5-11.5 years	2.51 (2.23-2.79)	2.41 (2.12-2.71)
11.5-16 years	4.21 (3.96-4.47)	4.19 (3.92-4.46)
Weight gain velocity z-score (standardized for sex and age)		
0-3 months	0.52 (0.33-0.71)	0.53 (0.33-0.73)
3-12 months	0.90 (0.70-1.09)	0.78 (0.58-0.99)
1-6.5 years	2.33 (2.14-2.51)	2.21 (2.00-2.42)
6.5-11.5 years	1.92 (1.71-2.12)	1.82 (1.60-2.04)
11.5-16 years	3.08 (2.90-3.27)	3.06 (2.86-3.25)
Conditional weight standardized residuals (standardized for sex and age)		
3 months	0.51 (0.34-0.69)	0.62 (0.44-0.81)
12 months	0.89 (0.72-1.07)	0.93 (0.72-1.11)
6.5 years	2.26 (2.08-2.43)	2.25 (2.05-2.44)
11.5 years	1.64 (1.46-1.81)	1.61 (1.42-1.79)
16 years	2.81 (2.64-2.99)	2.79 (2.61-2.98)

* Adjusted for child sex, sex-specific birth weight-for-gestational-age z-scores, and growth in preceding periods.

**Further adjusted for maternal and paternal characteristics, including maternal age, maternal and paternal height and BMI, East vs West geographic region, urban vs rural residence, and maternal education.

b. Diastolic blood pressure (mm Hg)

Analytic Approach	Partially-Adjusted Model*	Fully-Adjusted Model**
Absolute weight gain velocity (kg/mo)		
0-3 months	1.3 (0.5-2.0)	0.9 (0.2-1.7)
3-12 months	2.6 (1.2-4.0)	2.4 (0.9-3.9)
1-6.5 years	20.8 (18.0-23.6)	15.5 (13.7-21.4)
6.5-11.5 years	8.8 (7.5-10.0)	9.0 (7.6-10.3)
11.5-16 years	7.7 (6.8-8.5)	7.9 (7.0-8.8)
Change in sex-specific weight-for-age z-score		
0-3 months	0.24 (0.09-0.40)	0.17 (0.01-0.33)
3-12 months	0.28 (0.13-0.44)	0.25 (0.09-0.42)
1-6.5 years	1.11 (0.96-1.25)	0.97 (0.81-1.14)
6.5-11.5 years	1.39 (1.20-1.59)	1.45 (1.24-1.66)
11.5-16 years	1.60 (1.41-1.78)	1.68 (1.48-1.88)
Weight gain velocity z-score (standardized for sex and age)		
0-3 months	0.23 (0.10-0.36)	0.16 (0.03-0.31)
3-12 months	0.25 (0.12-0.38)	0.22 (0.08-0.37)
1-6.5 years	1.00 (0.87-1.34)	0.88 (0.73-1.03)
6.5-11.5 years	1.03 (0.88-1.76)	1.05 (0.90-1.21)
11.5-16 years	1.19 (1.06-1.33)	1.23 (1.09-1.38)
Conditional weight standardized residuals (standardized for sex and age)		
3 months	0.22 (0.09-0.35)	0.20 (0.06-0.33)
12 months	0.25 (0.12-0.38)	0.29 (0.15-0.42)
6.5 years	0.98 (0.85-1.10)	0.90 (0.76-1.05)
11.5 years	0.92 (0.79-1.04)	0.97 (0.83-1.10)
16 years	1.07 (0.94-1.20)	1.12 (0.98-1.25)

* Adjusted for child sex, sex-specific birth weight-for-gestational-age z-scores, and growth in preceding periods.

**Further adjusted for maternal and paternal characteristics, including maternal age, maternal and paternal height and BMI, East vs West geographic region, urban vs rural residence, and maternal education.

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