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Birth size, early life weight gain, and mid-childhood cardiometabolic health

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Abstract

Objective—To examine associations of birth size and weight gain during 4 early-life age intervals with mid-childhood adiposity and metabolic profile, and to evaluate for an interaction between birth size and early-life weight gain.

Study design—Using data from 963 participants of Project Viva, a U.S. pre-birth cohort, we used multivariable linear regression to examine relations of birth size (tertiles of birthweight-for-gestational-age z-score) and weight gain (BMI z-score [BMIZ] change) during 4 age intervals (birth–6 months, 6 months–1 year, 1 year–2 years, 2 years–3 years) with body composition and metabolic biomarkers during mid-childhood (6.6 years – 10.7 years).

Results—After accounting for confounders and previous growth, greater BMIZ change during all 4 age intervals corresponded with higher mid-childhood adiposity, with larger effect sizes for later (1–2y and 2–3y) vs. earlier (birth–6mo and 6mo–1y) timeframes. We observed effect modification by birth size for the birth–6mo and 6mo–1y intervals. Greater birth–6mo BMIZ change was associated with higher overall adiposity (0.40 [95% CI 0.29, 0.51] kg DXA total fat mass per z-score) among children in the highest birth size tertile. Similar associations were

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observed for central adiposity. Each increment in 6mo–1y BMIZ change corresponded with 0.55 (0.05, 1.05) units higher HOMA-IR and 2.68 (0.96, 4.40) ng/mL higher leptin among the smallest infants.

Conclusions—BMIZ gain after 1 year is associated with greater mid-childhood adiposity regardless of birth size, whereas the long-term influence of weight gain during the first postnatal year may depend on size at birth. Future studies are warranted to validate findings and examine relations with conventional birth size cut-offs.

Keywords

birth size; postnatal growth; childhood adiposity; cardiometabolic health

Pre- and postnatal weight gain patterns may influence future adiposity and metabolic risk. For example, lower birthweight is related to risk of diabetes^{1–3} and heart disease;⁴ higher birthweight predicts future obesity.⁵ Rapid postnatal weight gain, typically assessed during the first two years of life, is linked to obesity^{6–9} and hypertension,^{10, 11} with some^{12–14} studies indicating highest risk among infants who were also small at birth. However, the current evidence base contains important gaps. First, because most studies examined single time periods within the first two postnatal years,^{6, 15, 16} little is known regarding the relative importance of different early life age intervals. Assessing growth during specific timeframes is important considering that weight gain during the first 6 months primarily represents accrual of adiposity,¹⁷ whereas gains later in infancy correspond with fat-free mass.¹⁸ Thus, faster weight gain early in infancy may be a stronger determinant of future obesity and dysmetabolism. Second, many studies relied on body mass index (BMI) as the only indicator of adiposity later in life. Yet, BMI does not provide information on body composition or fat distribution, which have important implications for metabolic health.¹⁹ Finally, in addition to considering adiposity outcomes, it is important to assess metabolic biomarkers (e.g. glycemia, adipokines, lipids) as these risk factors track from early life into adulthood²⁰ and could manifest in non-overweight/obese youth.²¹

Our aims were twofold. First, we sought to elucidate relations of birth size and weight gain during four early life age intervals (birth to 6 months, 6 months to 1 year, 1 to 2 years, and 2 to 3 years) with mid-childhood adiposity and cardiometabolic health in Project Viva, an ongoing U.S. pre-birth cohort. Second, we aimed to determine whether the relationship between weight gain during each age interval and mid-childhood health differed by birth size, and if so, to further explore these associations in stratified analysis.

METHODS

This study included participants in Project Viva, an ongoing cohort study of pregnant women and their children, recruited from a group practice in Massachusetts (Atrius Harvard Vanguard Medical Associates). Details on recruitment, exclusion criteria, and study design have been published.²²

Of the 2,128 live singleton births, 1,708 mother-child pairs were eligible for the mid-childhood visit, of whom 65% (*n*=1116) attended an in-person visit at age 6–10 years

(median 7.7 y). We further excluded children whose mothers had type 1 or 2 diabetes ($n=16$) and those born <34 weeks ($n=45$) because we were interested in patterns of growth among healthy, term infants of mothers without preexisting metabolic complications. The final sample was composed of 963 participants for whom we had information on at least one of the mid-childhood outcomes, and BMI z-score (BMIZ) change during at least one of the age intervals; 331 participants had data on BMIZ change during all periods. The study sample was similar to those who attended the mid-childhood visit but were not included ($n=153$) in terms of income, parental BMI, parity, and education. However, the sample included a lower proportion of Black children (16% vs. 22%), higher proportion of mothers who smoked before pregnancy (20% vs. 13%), and lower proportion of those who smoked during pregnancy (9% vs. 17%). Mothers provided written informed consent at recruitment and at outcome assessment; children provided verbal assent in mid-childhood. The institutional review board of Harvard Pilgrim Health Care approved study protocols. All procedures were conducted according to ethical standards.

Delivery hospital medical records provided information on perinatal characteristics including the child's sex, birthweight, mode of delivery, and delivery date. We calculated gestational age at birth from the date of the last menstrual period or from a second trimester ultrasound if the estimated delivery date differed by >10 days. We determined sex-specific birth weight-for-gestational age z-scores (BWZ) based on U.S. national reference data.²³ Although birth size is typically classified as small-for-gestational-age (SGA: <10th percentile), appropriate-for-gestational-age (AGA: 10th percentile to <90th percentile), and large-for-gestational-age (LGA: 90th percentile), we categorized birth size in tertiles because of relatively few SGA births ($n=54$).

We obtained data on weight and length from a combination of medical records and research measures, using research standard measures when available. We abstracted weight at birth, 1 year, and 2 years from clinical records. At the 6 month and 3 year research visits, research assistants (RAs) measured weight to the nearest 0.1 kg on an electronic scale. For length at birth and 6 months, we used the recumbent length board technique.^{24, 25} We abstracted length at 1 and 2 years from clinical records and applied a corrective algorithm to account for systematic overestimation of length from the paper-and-pencil technique used in clinics.²⁴ At the 3 year research visit, RAs measured standing height to the nearest 0.1 cm on a stadiometer. We determined age- and sex-specific BMI z-scores using the World Health Organization (WHO) growth reference^{26, 27} and calculated BMIZ change during each age interval as the difference in attained BMIZ. Even though the optimal indicator of adiposity gain in infancy is not established, studies in school-age children have shown that prospective changes in BMIZ corresponds with fat growth.^{28, 29} Taking this in consideration with the high correlation between BMIZ and weight-for-length, a clinical measure of adiposity during infancy (Spearman's ρ at birth = 0.81, at 6 months = 0.99, at 1 year = 0.98, and at 2 years = 0.99), we used BMIZ change as an indicator for adiposity gain for all age intervals.

Outcomes: Mid-childhood body composition and metabolic biomarkers

At the mid-childhood visit, RAs measured the children's weight, height, and waist circumference using standard protocol.³⁰ We calculated age- and sex-specific BMI z-scores

(BMIZ) using the CDC 2000 growth reference.³¹ RAs administered whole body dual X-ray absorptiometry (DXA) scans with the Hologic model Discovery A (Hologic, Bedford, MA, USA). A single RA checked all scans for positioning, movement, and artifacts, and defined body regions for analysis (intra-rater reliability: $r=0.99$). DXA scans provided data on total fat mass, trunk fat mass, and fat-free mass (“lean mass”). We calculated fat mass index (FMI) as total fat mass (kg)/[height (m)]², fat-free mass index (FFMI) as total lean mass (kg)/[height (m)]², and % body fat as total fat mass/[total fat mass + total lean mass].

Using fasting blood, we measured plasma fasting insulin using an electrochemiluminescence immunoassay. Fasting glucose was measured enzymatically (Roche Diagnostics, Indianapolis, IN). We calculated insulin resistance using the homeostasis model assessment (HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405). Plasma leptin and adiponectin were measured via radioimmunoassay (Linco Research Inc., St Charles, MO).^{32, 33} We used an immunoturbidimetric high-sensitivity assay on a Hitachi 911 analyzer to determine C-reactive protein (hsCRP) concentrations. Plasma interleukin-6 (IL-6) was measured by ELISA. Lipids were measured enzymatically with correction for endogenous glycerol.

Statistical analyses

First, we examined the distributions of family and sociodemographic characteristics, as well as BMIZ change during the 4 age intervals, across tertiles of birth size to identify potential confounders. We natural log-(ln)-transformed hsCRP and IL-6 owing to non-normal distributions. In further analyses, we used the ln-transformed outcomes and calculated a percent change by using the exponential regression coefficients, subtracting by 1, and multiplying by 100.

We used multivariable linear regression to investigate the associations of birth size with mid-childhood body composition and metabolic profile. We first estimated mean differences and 95% confidence interval (95% CI) in each mid-childhood outcome according to tertiles of birth size, with the 2nd tertile as the referent. Next, we examined associations of continuous BMIZ gain during each age interval, separately, with the mid-childhood outcomes. The final models where birth size was the exposure of interest accounted child’s age, sex, race/ethnicity, breastfeeding duration, and maternal education. Further adjustment for maternal age, pre-pregnancy BMI, prenatal gestational diabetes status ($n=46$), physical activity prior to and during pregnancy, delivery method, or partner’s BMI did not change our findings; thus, we did not include these variables in the final models. We used similar models where BMIZ change was the exposure, but we also included continuous BWZ and BMIZ change during all previous age intervals. Adjustment for previous BMIZ change resulted in a decrease in sample size for the later timeframes; however, sociodemographic, perinatal, and mid-childhood characteristics were similar across the subsamples (Table I; available at www.jpeds.com). To determine whether associations between BMIZ change and mid-childhood outcomes were modified by birth size, we conducted a test for a statistical interaction by birth size tertiles. If there was evidence for interaction (P -interaction <0.05) we conducted additional analyses stratified by birth size for those age intervals.

Because the correlations between BMIZ change during the early life age intervals were moderately high for some periods (Table II; available at www.jpeds.com), we evaluated for multicollinearity using the variance inflation factor (VIF). VIF for all models were <2.5 , which is well below the standard cut-off of 10 which indicates high multicollinearity.³⁴

We also conducted sensitivity analyses. First, we assessed BMIZ change as a velocity (BMIZ change per year) because the age intervals were not all of equal length. Using velocities yielded similar results; therefore we present results for BMIZ change for ease of interpretation. Second, we restricted the analysis to the 331 participants with available data during all 4 age intervals and observed no material differences in the direction or magnitude of associations. Third, we excluded the 46 women with gestational diabetes because offspring of these women may exhibit altered body composition³⁵ and metabolic profile;³⁶ this analysis produced similar results, so we included these women in the final analysis.

Because some subjects were missing covariate information, we carried out imputation analyses. We generated 50 imputed datasets including data from all 2,128 Project Viva subjects in the process to obtain covariate information for the 963 participants in the study and combined estimates using PROC MIANALYZE (SAS Institute Inc.).³⁷ Only observed exposures (birth size and BMIZ change) were included in the analysis. For the outcomes, we imputed missing values for BMI z-score ($n=13$) and waist circumference ($n=11$) if the child attended the mid-childhood visit. We also imputed values for the cardiometabolic biomarkers (HOMA-IR: $n=137$, leptin and adiponectin: $n=185$, lipids: $n=202$; hsCRP and IL-6: $n=204$) if the child had a blood draw during the visit but was missing biomarker data. All children who participated in a DXA visit had scan results ($n=762$), thus DXA data were not imputed. The results from imputed data were not different from those of complete case – e.g. list-wise deletion – original data (data available upon request). All analyses were performed with use of the Statistical Analyses System software (version 9.3; SAS Institute Inc., Cary, NC).

Results

Birthweight-for-gestational age z-score (mean $\pm$ SD) among the 963 participants was 0.20 ± 0.95 . BMIZ change was 0.12 ± 1.30 for birth to 6 months, -0.08 ± 0.83 for 6 months to 1 year, -0.13 ± 0.95 for 1 to 2 years, and 0.29 ± 0.88 for 2 to 3 years. Children were 7.9 ± 0.8 years at the mid-childhood visit. Mid-childhood BMIZ was 0.37 ± 1.02 units, DXA total fat mass was 7.3 ± 3.7 kg, and DXA total lean mass was 21.5 ± 4.3 kg. We show additional mid-childhood characteristics in Table III. In unadjusted analyses, children of smaller birth size (e.g. lower BWZ) were born to younger, non-White, single mothers, with annual household income $<20K$. These smaller newborns also exhibited relatively fast BMIZ gain from birth to 6 months, in comparison with those in the 2nd and 3rd birth size tertiles.

After accounting for child's age, sex, race, and breastfeeding duration, larger birth size was related to higher mid-childhood adiposity according to DXA total fat mass (0.29 [95% CI: $0.04, 0.54$] kg per BWZ), BMI z-score (0.13 [95% CI: $0.07, 0.20$] z per BWZ), and waist circumference (1.09 [95% CI: $0.58, 1.59$] cm per BWZ), and greater lean mass (0.74 [95%

CI: 0.50, 0.99] kg per BWZ). We observed similar associations with tertiles of birth size (Table III).

In Table IV, we show the associations of BMIZ change during each age interval with mid-childhood outcomes from the adjusted analysis. Using multivariable models that included child's age, sex, race, breastfeeding duration, continuous BWZ, and BMIZ change during all previous age intervals, we observed a general trend that greater BMIZ change during each age interval was associated with greater mid-childhood adiposity, with larger point estimates during the later time frames. For example, each increment in BMIZ change from birth to 6 months, 6 months to 1 year, 1 to 2 years, and 2 to 3 years was associated with 0.57 (95% CI: 0.29, 0.85) kg, 0.41 (95% CI: 0.00, 0.83) kg, 0.71 (95% CI: 0.32, 1.10) kg, and 1.34 (95% CI: 0.94, 1.74) kg higher DXA total fat mass in mid-childhood, respectively. We found similar associations with DXA lean mass and fat-free mass index (FFMI), although we noted that greater BMIZ change was also associated with higher % body fat (Table IV), an indicator of relative fat mass. For the cardiometabolic biomarkers, we found a positive relation of BMIZ change from birth to 6 months with mid-childhood hsCRP levels (28% [95% CI: 8%, 51%] per unit BMIZ change).

We observed evidence of effect modification by birth size for adiposity outcomes with respect to the birth to 6 months and 6 months to 1 year age intervals. Table V displays associations of BMIZ change from birth to 6 months with mid-childhood outcomes within tertiles of birth size. More rapid BMIZ change during this period was related to higher overall and central adiposity, with larger point estimates among children who were larger infants. For example, each unit BMIZ gain during the first 6 postnatal months was associated with 0.29 (95% CI: -0.15, 0.73) kg, 0.44 (95% CI: 0.06, 0.94) kg, and 0.85 (95% CI: 0.33, 1.37) kg higher DXA total fat mass in mid-childhood for children in the 1st, 2nd, and 3rd birth size tertiles, respectively. Faster BMIZ gain was also directly related to lean mass, although the positive association with % fat mass suggests that weight gain during this time frame is more strongly related to fat mass. Among the largest infants, higher BMIZ change was associated with higher hsCRP (37.4% [95% CI: 4.2%, 81.3%] increase per unit BMIZ change) and IL-6 (17.3% [95% CI: 1.5%, 35.7%] per unit BMIZ change).

We also conducted stratified analyses for the 6 month to 1 year period (Table VI). Contrary to the other age intervals, more rapid weight gain from 6 months to 1 year predicted higher mid-childhood adiposity among the smallest infants, although as indicated in Table II, no statistically significant interaction was observed with birth size. Nevertheless, these trends are in line with findings for HOMA-IR and leptin, both of which are adiposity-associated metabolic biomarkers. Children in the lowest birth size tertile who gained weight faster from 6 months to 1 year exhibited higher HOMA-IR (0.55 [95% CI: 0.05, 1.05] per unit BMIZ change) and leptin (2.68 [95% CI: 0.96, 4.40] ng/mL per unit BMIZ change).

DISCUSSION

Contrary to older studies³⁸ as well as some recent investigations^{10, 39–41} we found that smaller infants did not have higher fat mass or % body fat in mid-childhood, regardless of postnatal weight gain patterns. These results are in line with that of the Promotion of

Breastfeeding Intervention Trial (PROBIT)⁴². Kramer et al reported that small-for-gestational age newborns did not have higher overall or central adiposity at 11.5 years of age regardless of weight gain trajectories, but rather, it was the larger infants who were predisposed for greater adiposity. The investigators speculated that the inconsistencies in literature may partially due to the fact that several of these studies^{43–47} adjusted for height, weight, and/or Tanner stage at the time of adiposity measurement, which could introduce (rather than reduce) bias by adjusting for variables on the causal pathway between the exposure and outcome.⁴⁸

We also observed larger estimates of association for weight gain during the toddler (1 to 2 years) and early childhood years (2 to 3 years) than for earlier age intervals. This contrasts with results from an analysis of electronic medical records from well-child visits between 1980 and 2008.¹⁵ In this study, Taveras et al reported that upwards crossing of 2 major weight-for-length percentiles during the first 6 months of life was more predictive of obesity at age 5 and 10 years than were crossings during later age intervals.¹⁵ Likewise, a study of Chinese children born between 2000 and 2005⁸ found that BMIZ gain during the first 3 months was more strongly related to obesity at 4–5 years than BMIZ gain from 2 to 2.5 years and 2.5 to 3 years.⁸ However, our findings do corroborate some published studies. In a retrospective study of 1,526 Indian adults born between 1969 and 1972, Sachdev et al found that higher BMI at birth, and increases in BMI during each subsequent age interval correlated with higher adult BMI, with larger effect sizes during late infancy and childhood.⁴⁹ Discrepancies in study findings could be due to differences in race/ethnicity, calendar time when the study was conducted, the timing and length of the early life age intervals, the metric used to quantify early life weight gain, age at outcome assessment, and inconsistent methods of analysis. Our findings emphasize the importance of examining the influence of weight gain trajectories beyond infancy.

Because we had serial length and weight measurements from birth through 3 years, we were able to evaluate for interactions between birth size and early weight gain during each timeframe. We noted that unlike the 1 to 2 year and 2 to 3 year age intervals, the associations for BMIZ gain during the first year of life differed with respect to birth size. Specifically, larger infants who gained weight faster from birth to 6 months had higher overall and central adiposity in mid-childhood. From 6 months to 1 year, smaller infants who gained weight more rapidly exhibited higher insulin resistance, as indicated by HOMA-IR, and possibly higher leptin. Although there was no statistical evidence for effect modification by birth size during this timeframe for the adiposity outcomes, we observed a similar relationship between BMIZ change and higher overall and central fat mass in mid-childhood among smaller infants. The parallel trends between the metabolic biomarkers and adiposity are noteworthy considering that adipose tissue can influence insulin⁵⁰ and adipocytokine⁵¹ levels. Therefore, the higher fat mass observed for smaller infants who gained weight faster from 6 months to 1 year may be driving the analogous associations for HOMA-IR and leptin.^{52, 53} One possible explanation for these findings is that weight gain patterns during different early life periods may have differential effects on acquisition of fat vs. fat-free mass. However, current evidence in this area is inconsistent, and comes predominantly from adult populations.^{18, 49, 54}

In addition to the above birth size-specific associations with metabolic biomarkers, we also found that faster weight gain from birth to 6 months corresponded with higher hsCRP during mid-childhood, with no notable differences by birth size. A possible reason for the overall null associations for the metabolic outcomes is that our study population is relatively young, and metabolic derangements may not manifest until later in the life course.

This study has some limitations. First, although Project Viva includes diverse racial and ethnic backgrounds, it represents a relatively well-educated and high-income population; thus, findings may not be generalizable to lower socioeconomic populations and developing country settings. Second, we did not have the exact same set of participants in each age interval, as the sample size depended on availability of anthropometric measures. This could limit comparability across the different periods of postnatal growth; however, characteristics of the 4 subsets of participants were very similar and restricting the analysis to participants with complete data during all age intervals yielded similar results. Third, although the CDC growth reference is recommended for BMI z-score calculations in children >2 years of age,⁵⁶ we used the WHO standard to maintain consistency with the earlier age intervals. Use of WHO vs. CDC growth charts may lead to higher estimates of overweight/obesity and lower estimates of underweight;⁵⁶ however, because we used continuous standardized BMI values to quantify growth, we expect that the relative rank between individuals is preserved regardless of the reference used. Fourth, BMIZ at birth was based clinical measures of weight, which is measured quite precisely, and research standard measures of length because clinical techniques (eg, paper- and-pencil) are less accurate and prone to systematic underestimation.²⁴ Although use of length from research measures may yield higher BMIZ values than calculations using clinical lengths,²⁴ we do not expect this to affect our results because we used BMIZ to calculate continuous change over time rather than for weight status classification. Further, we applied a correction factor to clinical lengths at 1 and 2 years to reduce discrepancies between clinical and research measures. Fifth, extremes of birth size carry different health risks; our study was underpowered to examine large-for-gestational age (LGA) and small-for-gestational age (SGA) babies separately. Because birth size was specific to our study sample, generalizability may be limited to populations with markedly different distributions of birth weight-for-gestational age. Finally, we cannot discount the possibility of chance findings given the large numbers of models tested. However, many of the mid-childhood outcomes are measurements of the same biological indicator, e.g. DXA total fat mass, fat mass index, and BMI z-score are measures of overall adiposity, and the fact that we observed similar associations across these outcomes supports the validity of our findings.

Our results suggest that obesity prevention should target children who gain weight more rapidly than their peers, particularly during the toddler/preschool years. Our findings also support the need for obesity-prevention and nutrition programs in preschool or childcare settings, as they may be feasible and effective strategies to prevent excess early weight gain on a larger scale.⁵⁷

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Abbreviations

BMIZ	body mass index z-score
DXA	dual x-ray absorptiometry
CRP	C-reactive protein
IL-6	Interleukin-6
HOMA-IR	homeostatic model assessment of insulin resistance
SGA	small for gestational age
LGA	larger for gestational age

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Table 1

Characteristics of Project Viva participants for subsamples during each age interval.

	Mean $\pm$ SD or % (N)			
	Birth – 6 mo <i>n</i> = 483	6 mo – 1 y <i>n</i> = 404	1 – 2 y <i>n</i> = 352	2 – 3 y <i>n</i> = 331
Maternal & perinatal characteristics				
Maternal age at enrollment	32.6 $\pm$ 5.2	32.4 $\pm$ 5.2	32.5 $\pm$ 5.2	32.6 $\pm$ 5.2
Single mother	7.5% (36)	7.2% (29)	7.1% (25)	7.0% (23)
Mother did not complete primary education	6.4% (31)	6.7% (27)	6.6% (23)	6.1% (20)
Annual household income <20k	2.8% (13)	2.6% (10)	2.1% (7)	2.2% (7)
Primiparous	47.6% (230)	48.8% (197)	48.3% (170)	48.6% (161)
Smoked during pregnancy	8.9% (43)	9.2% (37)	9.4% (33)	9.7% (32)
Gestational glucose tolerance				
Normoglycemic	83.6% (402)	84.3% (339)	84.3% (295)	84.8% (279)
Isolated hyperglycemia	8.5% (41)	7.7% (31)	7.7% (27)	8.2% (27)
Impaired glucose tolerance	3.7% (18)	4.0% (16)	4.0% (14)	4.0% (13)
Gestational diabetes	4.2% (20)	4.0% (16)	4.0% (14)	3.0% (10)
Child characteristics at birth				
Cesarean delivery	23.8% (115)	24.3% (98)	25.0% (88)	25.1% (83)
Male	49.1% (237)	47.5% (192)	48.0% (169)	47.4% (157)
Race/ethnicity				
Black	13.7% (66)	13.9% (56)	14.3% (50)	13.6% (45)
Hispanic	3.7% (18)	3.7% (15)	4.0% (14)	3.9% (13)
White	68.7% (331)	67.7% (273)	66.4% (233)	66.2% (219)
Asian	2.7% (13)	2.5% (10)	2.9% (10)	3.0% (10)
Other	11.2% (54)	12.2% (49)	12.5% (44)	13.3% (44)
Birthweight-for-gestational age z-score ^a	0.24 $\pm$ 0.97	0.24 $\pm$ 0.95	0.26 $\pm$ 0.96	0.23 $\pm$ 0.94
Breastfeeding <6 months	41.1 (197)	41.4 (166)	42.7 (150)	41.5 (137)
Postnatal BMI z-score change ^b				
Birth to 6 months	0.12 $\pm$ 1.30	0.12 $\pm$ 1.27	0.12 $\pm$ 1.30	0.13 $\pm$ 1.27
6 months to 1 year	−0.12 $\pm$ 0.83	−0.12 $\pm$ 0.83	−0.1 $\pm$ 0.83	−0.09 $\pm$ 0.83
1 year to 2 years	−0.09 $\pm$ 0.91	−0.09 $\pm$ 0.91	−0.09 $\pm$ 0.91	−0.13 $\pm$ 0.93
2 years to 3 years	0.26 $\pm$ 0.89	0.23 $\pm$ 0.87	0.26 $\pm$ 0.89	0.29 $\pm$ 0.88
Child characteristics during mid-childhood				
Age (y)	7.8 $\pm$ 0.8	7.8 $\pm$ 0.8	7.8 $\pm$ 0.8	7.7 $\pm$ 0.7
DXA fat mass (kg)	7.1 $\pm$ 3.6	6.9 $\pm$ 3.1	7.0 $\pm$ 3.2	6.8 $\pm$ 2.8
Fat mass index (kg/m ²)	4.3 $\pm$ 1.8	4.2 $\pm$ 1.7	4.3 $\pm$ 1.7	4.2 $\pm$ 1.6
BMI-for-age z-score	0.33 $\pm$ 0.98	0.33 $\pm$ 0.95	0.32 $\pm$ 0.99	0.29 $\pm$ 0.97
DXA trunk fat mass (kg)	2.4 $\pm$ 1.6	2.3 $\pm$ 1.4	2.3 $\pm$ 1.4	2.2 $\pm$ 1.2
Waist circumference (cm)	59.2 $\pm$ 7.9	59.0 $\pm$ 7.4	59.0 $\pm$ 7.7	58.4 $\pm$ 6.7
DXA total lean mass (kg)	21.0 $\pm$ 3.8	20.8 $\pm$ 3.4	20.8 $\pm$ 3.4	20.6 $\pm$ 3.1

	Mean $\pm$ SD or % (N)			
	Birth – 6 mo	6 mo – 1 y	1 – 2 y	2 – 3 y
	<i>n</i> = 483	<i>n</i> = 404	<i>n</i> = 352	<i>n</i> = 331
Fat-free mass index (kg/m ²)	12.8 $\pm$ 1.3	12.8 $\pm$ 1.2	12.8 $\pm$ 1.2	12.7 $\pm$ 1.1
% Body fat	24.4 $\pm$ 6.2	24.3 $\pm$ 6.0	24.4 $\pm$ 6.1	24.1 $\pm$ 5.9
HOMA-IR	1.87 $\pm$ 1.99	1.84 $\pm$ 1.67	1.80 $\pm$ 1.69	1.73 $\pm$ 1.58
Leptin (ng/mL)	5.4 $\pm$ 7.0	5.2 $\pm$ 6.8	5.2 $\pm$ 7.0	4.7 $\pm$ 5.5
Adiponectin (μ g/mL)	15.8 $\pm$ 9.1	15.9 $\pm$ 9.5	15.9 $\pm$ 9.4	16.3 $\pm$ 9.4
Triglycerides (mg/dL)	61.0 $\pm$ 48.0	61.7 $\pm$ 50.9	62.9 $\pm$ 53.7	59.0 $\pm$ 23.2
Total cholesterol (mg/dL)	161.5 $\pm$ 27.2	162.5 $\pm$ 27.4	163.4 $\pm$ 27.9	163.3 $\pm$ 28.2
HDL (mg/dL)	57.1 $\pm$ 13.1	57.0 $\pm$ 13.3	56.7 $\pm$ 13.2	57.2 $\pm$ 13.1
LDL (mg/dL)	92.2 $\pm$ 20.1	93.1 $\pm$ 23.9	94.1 $\pm$ 24.6	94.3 $\pm$ 24.2
hsCRP (mg/L)	0.74 $\pm$ 2.11	0.73 $\pm$ 2.11	0.60 $\pm$ 1.26	0.58 $\pm$ 1.26
IL-6 (pg/mL)	0.99 $\pm$ 1.20	1.02 $\pm$ 1.27	1.00 $\pm$ 1.25	0.98 $\pm$ 1.27

^aAccording to US natality reference data.²³

^bCalculated as the difference between attained BMI z-score according to WHO reference data between each age.^{26, 27}

Spearman’s correlation coefficients between BMIZ change during 4 early life age intervals

Table 2

BMIZ change	Birth – 6 mo			
	Birth – 6 mo	6 mo – 1 y	1 – 2 y	2 – 3 y
Birth – 6 mo	1.00 n = 483			
6 mo – 1 y	–0.37 n = 404	1.00 n = 671		
1 – 2 y	–0.10 n = 352	–0.28 n = 574	1.00 n = 773	
2 – 3 y	0.00 n = 343	–0.05 n = 533	–0.61 n = 689	1.00 n = 715

Table 3

Associations of birthweight-for-gestational-age z-score (BWZ) tertiles with mid-childhood adiposity and cardiometabolic health

Unadjusted analysis: Mean ± SD for mid-childhood outcomes										Multivariable analysis: β (95% CI) in mid-childhood outcomes ^a			
	Overall n = 963	Tertiles of BWZ			P	Per unit BWZ n = 963	Tertiles of BWZ			P			
		Tertile 1 n = 321	Tertile 2 n = 316	Tertile 3 n = 326			Tertile 1 n = 321	Tertile 2 n = 316	Tertile 3 n = 326				
Mid-childhood body composition													
Overall adiposity													
DXA fat mass (kg)	7.3 ± 3.7	7.24 ± 3.95	7.13 ± 3.41	7.6 ± 3.8	0.51	0.29 (0.04, 0.54)	-0.04 (-0.62, 0.55)	0.00 (Reference)	0.65 (0.07, 1.23)	0.03			
Fat mass index (kg/m ²)	4.4 ± 1.9	4.4 ± 2.1	4.2 ± 1.7	4.5 ± 1.9	0.51	0.09 (-0.05, 0.22)	0.12 (-0.19, 0.43)	0.00 (Reference)	0.35 (0.04, 0.66)	0.08			
BMI-for-age Z-score	0.37 ± 1.02	0.29 ± 1.11	0.32 ± 0.95	0.50 ± 0.97	0.02	0.13 (0.07, 0.20)	-0.06 (-0.21, 0.09)	0.00 (Reference)	0.21 (0.06, 0.36)	0.001			
Central Adiposity													
DXA trunk fat mass (kg)	2.5 ± 1.6	2.5 ± 1.8	2.4 ± 1.5	2.5 ± 1.6	0.75	0.08 (-0.04, 0.19)	0.05 (-0.21, 0.31)	0.00 (Reference)	0.20 (-0.05, 0.46)	0.27			
Waist circumference (cm)	59.8 ± 8.2	59.2 ± 8.7	59.4 ± 7.5	60.9 ± 8.2	0.02	1.09 (0.58, 1.59)	-0.51 (-1.68, 0.65)	0.00 (Reference)	1.67 (0.52, 2.83)	0.0005			
Lean mass													
DXA total lean mass (kg)	21.5 ± 4.3	21.0 ± 4.4	21.5 ± 4.3	22.0 ± 4.1	0.17	0.74 (0.50, 0.99)	-0.91 (-1.47, -0.34)	0.00 (Reference)	0.63 (0.07, 1.20)	<0.0001			
Fat-Free Mass Index (kg/m ²)	13.0 ± 1.4	12.9 ± 1.5	12.9 ± 1.3	13.1 ± 1.4	0.49	0.16 (0.06, 0.26)	-0.12 (-0.34, 0.10)	0.00 (Reference)	0.22 (0.00, 0.44)	0.009			
Relative fat mass													
% Body fat	24.5 ± 6.3	24.5 ± 6.4	24.1 ± 5.83	24.9 ± 6.5	0.59	0.14 (-0.29, 0.57)	0.50 (-0.49, 1.50)	0.00 (Reference)	1.04 (0.06, 2.03)	0.12			
Mid-childhood cardiometabolic outcomes													
HOMA-IR	1.83 ± 1.77	1.8 ± 1.5	2.00 ± 2.25	1.71 ± 1.52	0.26	0.03 (-0.11, 0.17)	-0.26 (-0.60, 0.08)	0.00 (Reference)	-0.23 (-0.57, 0.10)	0.26			
Leptin (ng/mL)	5.9 ± 7.5	6.0 ± 7.7	5.6 ± 6.6	5.9 ± 8.0	0.86	0.04 (-0.57, 0.65)	0.20 (-1.27, 1.66)	0.00 (Reference)	0.52 (-0.88, 1.92)	0.76			
Adiponectin (μg/mL)	15.5 ± 9.1	15.1 ± 9.1	15.2 ± 9.1	16.1 ± 8.9	0.47	0.54 (-0.22, 1.29)	-0.14 (-1.93, 1.66)	0.00 (Reference)	0.75 (-1.02, 2.52)	0.55			
Triglycerides (mg/dL)	57.8 ± 33.1	60.0 ± 28.7	55.5 ± 23.9	54.7 ± 25.5	0.23	-1.96 (-4.15, 0.24)	4.31 (-0.79, 9.41)	0.00 (Reference)	1.23 (-3.77, 6.23)	0.23			
Total cholesterol (mg/dL)	160.3 ± 36.0	162.7 ± 32.0	158.6 ± 27.3	159.5 ± 26.5	0.34	-1.86 (-4.31, 0.59)	3.55 (-2.13, 9.22)	0.00 (Reference)	0.34 (-5.11, 5.79)	0.39			
HDL (mg/dL)	52.2 ± 17.9	57.7 ± 14.9	56.7 ± 13.6	57.2 ± 13.6	0.80	0.08 (-1.11, 1.28)	0.77 (-1.96, 3.49)	0.00 (Reference)	0.55 (-2.13, 3.23)	0.85			
LDL (mg/dL)	91.5 ± 30.4	93.0 ± 27.3	90.8 ± 23.9	90.8 ± 22.0	0.57	-1.55 (-3.63, 0.52)	1.92 (-2.94, 6.77)	0.00 (Reference)	-0.46 (-5.14, 4.22)	0.57			
% Difference (95% CI) in mid-childhood outcomes ^a													
hsCRP (mg/L) ^b	0.9 ± 2.6	1.0 ± 2.8	0.9 ± 3.0	0.8 ± 2.1	0.80	0.3 (-5.0, 25.8)	-10.3 (-36.2, 26.0)	0.00 (Reference)	11.8 (-19.4, 55.1)	0.41			

	Unadjusted analysis: Mean $\pm$ SD for mid-childhood outcomes				Multivariable analysis: β (95% CI) in mid-childhood outcomes ^a			
	Tertiles of BWZ			P	Tertiles of BWZ			P
	Overall n = 963	Tertile 1 n = 321	Tertile 2 n = 316	Tertile 3 n = 326	Per unit BWZ n = 963	Tertile 1 n = 321	Tertile 2 n = 316	Tertile 3 n = 326
IL-6 (pg/mL) ^b	1.0 $\pm$ 1.5	0.9 $\pm$ 1.1	1.1 $\pm$ 1.8	1.0 $\pm$ 1.6	7.2 (-0.4, 15.4)	-9.7 (-24.3, 7.7)	0.00 (Reference)	1.9 (-14.4, 21.2)
				0.37				0.34

^aEstimates represent mean differences and 95% CI adjusted by child's age, sex, race, and breastfeeding duration.

^bIn the multivariable analysis, we used ln-transformed hsCRP and IL-6 and calculated % change by exponentiating regression coefficients, subtracting by 1, and multiplying by 100.

Table 4

Associations of BMI z-score (BMIZ) change during 4 early life age intervals with mid-childhood cardiometabolic health

	Birth – 6 mo <i>n</i> = 483	<i>P</i> -interaction with birth size	6 mo – 1 y <i>n</i> = 404	<i>P</i> -interaction with birth size	1 – 2 y <i>n</i> = 352	<i>P</i> -interaction with birth size	2 – 3 y <i>n</i> = 331	<i>P</i> -interaction with birth size
<i>6 (95% CI) for mid-childhood outcomes per 1 unit BMIZ change during each age interval^a</i>								
Mid-childhood body composition								
<i>Overall adiposity</i>								
DXA fat mass (kg)	0.57 (0.29, 0.85)	0.61	0.41 (0.00, 0.83)	0.51	0.71 (0.32, 1.10)	0.76	1.34 (0.94, 1.74)	0.19
Fat mass index (kg/m ²)	0.33 (0.18, 0.48)	0.60	0.18 (–0.05, 0.41)	0.39	0.38 (0.17, 0.60)	0.66	0.81 (0.58, 1.04)	0.23
BMI-for-age Z-score	0.25 (0.18, 0.32)	0.02	0.20 (0.09, 0.32)	0.45	0.21 (0.10, 0.32)	0.45	0.58 (0.45, 0.70)	0.08
<i>Central adiposity</i>								
DXA trunk fat mass (kg)	0.19 (0.06, 0.32)	0.46	0.16 (–0.03, 0.35)	0.50	0.32 (0.15, 0.50)	0.91	0.57 (0.39, 0.74)	0.23
Waist circumference (cm)	1.33 (0.76, 1.91)	0.09	1.69 (0.83, 2.55)	0.54	1.82 (1.01, 2.63)	0.20	2.95 (2.02, 3.89)	0.09
<i>Lean mass</i>								
DXA total lean mass (kg)	0.66 (0.41, 0.91)	0.60	0.64 (0.26, 1.01)	0.83	0.63 (0.30, 0.96)	0.77	0.77 (0.40, 1.15)	0.58
Fat-free mass index (kg/m ²)	0.31 (0.21, 0.41)	0.28	0.14 (–0.01, 0.29)	0.96	0.24 (0.10, 0.38)	0.91	0.45 (0.29, 0.61)	0.60
<i>Relative fat mass</i>								
% Body fat	0.95 (0.46, 1.44)	0.78	0.65 (–0.14, 1.44)	0.29	1.17 (0.42, 1.91)	0.54	2.57 (1.72, 3.42)	0.23
Mid-childhood cardiometabolic biomarkers^b								
HOMA-IR	–0.01 (–0.19, 0.18)	0.02	0.09 (–0.17, 0.35)	0.003	–0.02 (–0.27, 0.23)	0.31	0.14 (–0.17, 0.46)	0.16
Leptin (ng/mL)	0.32 (–0.39, 1.04)	0.51	0.45 (–0.59, 1.50)	0.06	0.08 (–1.04, 1.19)	0.67	0.89 (–0.37, 2.16)	0.56
Adiponectin (µg/mL)	–0.17 (–1.15, 0.81)	0.74	–0.09 (–1.63, 1.44)	0.18	0.30 (–1.23, 1.84)	0.62	–1.10 (–3.29, 1.09)	0.85
Triglycerides (mg/dL)	–0.18 (–2.82, 2.45)	0.48	–0.13 (–4.24, 3.98)	0.53	2.40 (–1.63, 6.42)	0.68	–0.81 (–5.82, 4.19)	0.59
Total cholesterol (mg/dL)	–0.99 (–3.82, 1.85)	0.89	–1.01 (–5.60, 3.57)	0.57	0.56 (–4.01, 5.13)	0.77	5.24 (–0.80, 11.28)	0.37
HDL (mg/dL)	–0.76 (–2.13, 0.60)	0.57	–0.50 (–2.77, 1.77)	0.66	–0.91 (–3.02, 1.19)	0.31	2.27 (–0.45, 5.00)	0.37
LDL (mg/dL)	–0.19 (–2.67, 2.30)	0.99	–0.49 (–4.41, 3.44)	0.32	0.99 (–2.97, 4.96)	0.98	3.13 (–2.15, 8.41)	0.45
<i>% Difference (95% CI) for mid-childhood outcomes per 1 unit BMIZ change during each postnatal period^a</i>								
hsCRP (mg/L) ^b	27.8 (8.3, 50.8)	0.94	22.9 (–4.7, 58.4)	0.95	15.7 (–9.5, 47.9)	0.34	18.7 (–13.6, 63.0)	0.51
IL-6 (pg/mL) ^b	7.7 (–1.4, 17.8)	0.71	2.7 (–10.4, 17.7)	0.80	–9.6 (–20.8, 3.1)	0.56	–1.3 (–18.5, 19.7)	0.95

^gEstimates represent mean differences and 95% CI adjusted by child's age, sex, race, breastfeeding duration, maternal education, continuous birthweight-for-gestational age z-score, and BMI z-score change during all previous growth period(s).

^hWe used ln-transformed hsCRP and IL-6 and calculated % change by exponentiating regression coefficients, subtracting by 1, and multiplying by 100.

Table 5

Associations of BMI z-score (BMIZ) change from birth to 6 months with mid-childhood body composition and cardiometabolic health, within tertiles of birth size among 483 Project Viva children

	Tertiles of birthweight z-score		
	Tertile 1	Tertile 2	Tertile 3
<i>6 (95% CI) in mid-childhood outcome^a</i>			
<i>Mid-childhood body composition</i>			
<i>Overall adiposity</i>			
DXA fat mass (kg)	0.29 (−0.15, 0.73)	0.44 (−0.06, 0.94)	0.85 (0.33, 1.37)
Fat mass index (kg/m ²)	0.19 (−0.05, 0.43)	0.25 (−0.02, 0.52)	0.48 (0.20, 0.75)
BMI-for-age Z-score	0.16 (0.03, 0.29)	0.22 (0.07, 0.37)	0.40 (0.29, 0.51)
<i>Central adiposity</i>			
DXA trunk fat mass (kg)	0.01 (−0.19, 0.21)	0.14 (−0.08, 0.36)	0.35 (0.10, 0.59)
Waist circumference (cm)	0.71 (−0.19, 1.62)	0.99 (−0.06, 2.05)	2.33 (1.33, 3.32)
<i>Lean mass</i>			
DXA total lean mass (kg)	0.48 (0.09, 0.88)	0.56 (0.10, 1.02)	0.83 (0.39, 1.27)
Fat-free mass index (kg/m ²)	0.22 (0.04, 0.40)	0.27 (0.11, 0.44)	0.42 (0.25, 0.60)
<i>Relative lean vs. fat mass</i>			
Lean-to-fat mass ratio	−0.14 (−0.28, 0.00)	−0.17 (−0.32, −0.01)	−0.21 (−0.34, −0.07)
% body fat	0.60 (−0.20, 1.40)	0.74 (−0.18, 1.66)	1.35 (0.48, 2.22)
<i>Mid-childhood metabolic profile</i>			
HOMA-IR	−0.19 (−0.44, 0.07)	0.19 (−0.32, 0.69)	0.09 (−0.07, 0.26)
Leptin (ng/mL)	0.22 (−0.86, 1.30)	0.92 (−0.16, 1.99)	−0.07 (−1.52, 1.37)
Adiponectin (μg/mL)	0.20 (−1.38, 1.78)	0.20 (−1.67, 2.07)	−0.42 (−2.01, 1.17)
Triglycerides (mg/dL)	−2.04 (−6.46, 2.38)	0.19 (−4.48, 4.86)	1.68 (−2.59, 5.94)
Total cholesterol (mg/dL)	−0.33 (−5.18, 4.51)	−1.79 (−6.87, 3.28)	−0.87 (−5.60, 3.87)
HDL (mg/dL)	0.88 (−1.27, 3.03)	−1.45 (−4.17, 1.27)	−1.57 (−3.81, 0.66)
LDL (mg/dL)	−0.81 (−5.10, 3.49)	−0.38 (−4.97, 4.21)	0.37 (−3.63, 4.38)
<i>% Difference (95% CI) in mid-childhood outcome^a</i>			
hsCRP (mg/L) ^b	13.4 (−14.6, 50.5)	24.2 (−8.4, 68.3)	37.4 (4.2, 81.3)
IL-6 (pg/mL) ^b	0.01 (−11.9, 13.5)	7.3 (−10.8, 29.2)	17.3 (1.5, 35.7)

^aEstimates represent mean differences and 95% CI adjusted by child's age, sex, race/ethnicity, breastfeeding duration, maternal education, and continuous birthweight z-score.

^bWe used ln-transformed hsCRP and IL-6 and calculated % change by exponentiating regression coefficients, subtracting by 1, and multiplying by 100.

Table 6

Associations of BMI z-score (BMIZ) change from 6 months to 1 year with mid-childhood body composition and cardiometabolic health, within tertiles of birth size for 404 Project Viva Children

	Tertiles of birthweight-for-gestational-age z-score		
	Tertile 1	Tertile 2	Tertile 3
	Mean difference (95% CI) in mid-childhood outcome ^a		
<i>Mid-childhood body composition</i>			
<i>Overall adiposity</i>			
DXA fat mass (kg)	0.63 (−0.10, 1.32)	0.43 (−0.18, 1.03)	0.06 (−0.79, 0.90)
Fat mass index (kg/m ²)	0.35 (−0.05, 0.75)	0.18 (−0.16, 0.52)	−0.06 (−0.51, 0.40)
BMI-for-age Z-score	0.23 (0.02, 0.45)	0.23 (0.02, 0.43)	0.14 (−0.04, 0.32)
<i>Central adiposity</i>			
DXA trunk fat mass (kg)	0.19 (−0.14, 0.53)	0.17 (−0.08, 0.42)	0.03 (−0.36, 0.42)
Waist circumference (cm)	1.93 (0.42, 3.43)	0.99 (−0.42, 2.42)	1.86 (0.39, 3.34)
<i>Lean mass</i>			
DXA total lean mass (kg)	0.29 (−0.34, 0.92)	0.78 (0.21, 1.36)	0.85 (0.11, 1.59)
Fat-free mass index (kg/m ²)	0.06 (−0.23, 0.35)	0.21 (−0.01, 0.43)	0.19 (−0.10, 0.49)
<i>Relative lean vs. fat mass</i>			
Lean-to-fat mass ratio	−0.33 (−0.57, −0.09)	−0.14 (−0.35, 0.08)	0.01 (−0.23, 0.25)
% body fat	1.49 (0.11, 2.87)	0.53 (−0.70, 1.77)	−0.31 (−1.85, 1.23)
<i>Mid-childhood metabolic profile</i>			
HOMA-IR	0.55 (0.05, 1.05)	−0.10 (−0.66, 0.46)	−0.25 (−0.52, 0.03)
Leptin (ng/mL)	2.68 (0.96, 4.40)	0.09 (−1.46, 1.63)	−0.97 (−2.98, 1.05)
Adiponectin (μg/mL)	−1.93 (−4.76, 0.90)	−1.29 (−3.97, 1.40)	1.19 (−1.21, 3.59)
Triglycerides (mg/dL)	−3.63 (−11.55, 4.29)	4.51 (−2.60, 11.62)	−0.52 (−7.38, 6.34)
Total cholesterol (mg/dL)	−0.81 (−10.11, 8.49)	2.80 (−4.80, 10.39)	−4.36 (−12.25, 3.54)
HDL (mg/dL)	0.82 (−3.31, 4.96)	−3.13 (−7.07, 0.81)	−0.47 (−4.31, 3.37)
LDL (mg/dL)	−0.91 (−9.18, 7.36)	5.02 (−1.30, 11.35)	−3.78 (−10.33, 2.77)
	<i>% Difference (95% CI) in mid-childhood outcome^a</i>		
hsCRP (mg/L) ^b	26.8 (−20.2, 101.5)	26.9 (−23.1, 109.6)	14.7 (−22.0, 68.7)
IL-6 (pg/mL) ^b	8.6 (−13.1, 35.6)	−8.0 (−31.2, 23.1)	−1.7 (−19.3, 19.8)

^aEstimates represent mean differences and 95% CI adjusted by child's age, sex, race/ethnicity, breastfeeding duration, maternal education, continuous birthweight z-score, and BMI z-score change from birth to 6 months.

^bWe used ln-transformed hsCRP and IL-6 and calculated % change by exponentiating regression coefficients, subtracting by 1, and multiplying by 100.