Weight Gain in Infancy and Vascular Risk Factors in Later Childhood

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KEY WORDS: carotid intima-media thickness, obesity, blood pressure, inflammation, risk factor.

ABBREVIATIONS: CI—confidence interval; DBP—diastolic blood pressure; HDL-C—high-density lipoprotein cholesterol; hsCRP—high-sensitivity C-reactive protein; IMT—intima-media thickness; OR—odds ratio; SBP—systolic blood pressure.

Dr. Skilton conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Marks contributed to the design and conduct of the Childhood Asthma Prevention Study (CAPS), contributed to the design and conduct of the cardiovascular substudy, reviewed and revised the manuscript, and approved the final manuscript as submitted. Drs. Ayer and Harmer contributed to the design and conduct of the cardiovascular substudy, reviewed and revised the manuscript, and approved the final manuscript as submitted. Ms. Garden and Drs. Garnett, Toelle, and Baur contributed to the interpretation of data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Leeder contributed to the design and conduct of the CAPS, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Webb contributed to the design and conduct of the CAPS, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Celermajer contributed to the design and conduct of the cardiovascular substudy, conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

WHAT’S KNOWN ON THIS SUBJECT: Excessive weight gain over the first 18 months of life may have consequences for later body size. However, the relationship of weight gain in this period to atherogenic risk factors in later childhood is not well characterized.

WHAT THIS STUDY ADDS: Early postnatal weight gain from birth to 18 months is independently associated with childhood overweight and obesity, excess central adiposity, and greater arterial wall thickness at age 8 years.

abstract

OBJECTIVE: We hypothesized that early weight gain would be associated with incident obesity, higher blood pressure, systemic inflammation, and arterial wall thickening in later childhood.

METHODS: A longitudinal birth cohort was recruited antenatally from 2 maternity hospitals in Sydney, Australia, between September 1997 and December 1999. Three hundred ninety-five nondiabetic children who were followed to age 8 years had complete data for early weight gain and arterial wall thickness.

RESULTS: Independent predictors of excess early weight gain (age 0–18 months; adjusted for height gain) included male gender (0.411 kg [SE: 0.121 kg [SE: 0.044] per week, \( P = .006 \)), birth length (0.156 kg [SE: 0.024] per cm, \( P < .001 \)), and failure to breastfeed to 6 months of age (0.498 kg [SE: 0.108], \( P < .001 \)). Early height-adjusted weight gain was significantly associated with later childhood overweight (odds ratio [OR]: 1.67 [95% confidence interval (CI): 1.26 to 2.20] per kg) and obesity (OR: 2.07 [95% CI: 1.53 to 2.79] per kg), excess central adiposity (OR: 1.54 [95% CI: 1.20 to 1.98] per kg), higher systolic blood pressure (1.24 mm Hg [SE: 0.33] per kg, \( P < .001 \)), higher C-reactive protein (0.17 mg/dL [SE: 0.06] per 100% increase in weight gain, \( P = .006 \)), and greater carotid intima-media thickness (0.012 mm [SE: 0.004] per kg, \( P = .002 \)).

CONCLUSIONS: Early postnatal weight gain from birth to age 18 months is significantly associated with later childhood overweight and obesity, excess central adiposity, and greater arterial wall thickness. *Pediatrics* 2013;131:e1821–e1828.

(Continued on last page)
The first 18 months of postnatal life are an important period for growth and development. It is a time of marked cell hyperplasia and maximal weight gain,1,2 culminating in a body weight >3 times that at birth.3 Changes in weight gain over this critical period may well have important consequences for body size in later life,4 and possibly in determining or influencing the risk of disease, in much the same way as obesity and vascular risk factors in mid- and late childhood appear to be significant predictors of adult risk of cardiovascular events.5,6 The determinants of weight gain in infancy and its relationship to atherogenic risk factors in later childhood, however, have not been well characterized.

We have previously studied in detail a group of several hundred community-based children through gestation, infancy, and early childhood, documenting changes in body size and certain vascular risk factors and measuring arterial structure and function at age 8 years.7,8 In particular, we were interested in assessing carotid intima-media thickness (IMT), a marker of atherosclerotic extent and an independent determinant of cardiovascular risk in adulthood.9 We therefore hypothesized that early weight gain, from birth to age 18 months would be associated with incident obesity, higher blood pressure, an adverse lipid profile, systemic inflammation, and arterial wall thickening in later childhood. In addition, we sought to determine the factors associated with early weight gain.

METHODS
Participants
This study reports the results in 395 nondiabetic children who had been enrolled before birth (between September 1997 and December 1999) in the Childhood Asthma Prevention Study, a 5-year randomized controlled trial after birth, to determine whether dietary omega-3 supplementation and/or house dust mite reduction may reduce the incidence of atopy and/or asthma in “at risk” children.10 Participants were considered “at risk” on the basis of having at least 1 parent or sibling with symptoms of asthma as assessed by a screening questionnaire. Exclusion criteria included infants from a multiple birth pregnancy and those born before 36 weeks’ gestation. In this trial, participants were studied at birth (n = 616) and at 18 months (n = 554), 3 years, and 5 years (n = 516) of age.11 They were subsequently followed up at age 8 years as part of an ongoing longitudinal cohort consisting of the original randomized trial participants. Vascular risk factors and carotid IMT were assessed only at the 8-year visit. We have previously shown that these trial interventions did not alter any vascular risk factors or body size measurements in these children.12 Two participants with clinically established type 1 diabetes were prospectively excluded. The current study reports results from those 395 nondiabetic children followed to age 8 years who had complete data for early postnatal weight gain and carotid IMT. Compared with those participants who were not included in the current analysis, the children reported here had older parents and their mothers were more likely to have a tertiary education (Supplemental Table 4).

This study was approved by the human research ethics committees of the University of Sydney, The Children’s Hospital at Westmead, and Sydney South West Area Health Service. The parent or legal guardian of each participating child provided written informed consent before taking part in the study.

Anthropometric Measurements and Cardiovascular Risk Factors
Birth weight and length were systematically recorded from hospital records, and this information was available for all participants. The Ponderal index was calculated as birth weight/length.5,13 Subsequent anthropometric measures were assessed at dedicated study visits.

Weight was measured to the nearest 0.1 kg by using calibrated electronic scales; height was measured to the nearest 0.5 cm by using a stadiometer; and waist circumference was measured at end expiration midway between the lower margin of the ribs and the iliac crest.14 BMI z score at age 8 years, weight-for-length at birth, and weight-for-height at age 18 months were calculated on the basis of US growth charts from the Centers for Disease Control and Prevention.15 Weight-for-length z score was unable to be calculated for 1 participant with a birth length of <45 cm. Waist-to-height ratio was calculated as a measure of central adiposity.

Additional consent to obtain a non-fasting blood sample at age 8 years was obtained for 319 participants (81%). Total and high-density lipoprotein cholesterol (HDL-C) were measured by standard enzymatic procedures, and high-sensitivity C-reactive protein (hsCRP) measured by an immunoturbidimetric method (Roche Diagnostics, Castle Hill, Australia). Non–HDL-C was calculated as total cholesterol minus HDL-C. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the brachial arterial, with the participant lying in a supine position after a 10-minute rest, by using a validated oscillometric device (Vital Signs Monitor; Welch Allyn, Skaneateles Falls, NY). The appropriate cuff size (small child, child, small adult, adult, large adult, or thigh) was determined by using the manufacturer’s...
artery index marker and range as printed on the cuff. The average of 2 measures, 10 minutes apart, was used for analysis. A third measure was obtained if the first 2 measures differed by >10 mm Hg.

National Heart, Lung, and Blood Institute criteria were used to define overweight (BMI: 85th–95th percentile) and obesity (BMI ≥95th percentile). Excess central adiposity was defined as a waist-to-height ratio ≥0.50.17,18

Carotid IMT
Carotid IMT was measured by using high-resolution ultrasound, as previously described. Briefly, high-resolution ultrasound images of the carotid arteries were obtained in longitudinal section. Carotid IMT was measured 0 to 1 cm proximal to the carotid bulb, at end-diastole, from 3 cardiac cycles in both the left and right carotid arteries. The single thickest point of the carotid IMT from either the right or left carotid was used for analysis, based on previous evidence that the maximum carotid IMT may be of greater relevance to later cardiovascular disease risk and our previous finding that associations of cardiovascular risk factors with maximum IMT in children are stronger than for mean IMT. Similar results were obtained if mean carotid IMT values were used in analysis (results not shown).

Parental Characteristics
Maternal age, parity, education, and smoking status during pregnancy were assessed by standardized questionnaire during a home visit by study personnel ~4 weeks before delivery. Additional home visits were undertaken at 1, 3, and 6 months after birth, during which breastfeeding status was recorded by questionnaire. Maternal and paternal height and weight were assessed directly at the 8-year visit. In cases in which only 1 parent attended the study visit, a self-reported measure was obtained from the nonattending partner via telephone. Complete maternal and paternal anthropometric measures were obtained for 376 and 360 participants, respectively.

Statistical Analyses
Weight gain during the first 18 months of postnatal life was described as follows: “weight gain,” the unadjusted difference between weight at 18 months and weight at birth; “height-adjusted weight gain,” the residual of weight gain from birth to 18 months on the change in height over the same period derived from gender-stratified linear regression; and “change in weight-for-height z score.” The 2 latter variables account for weight gain attributable to concurrent stature growth. Height-adjusted weight gain is expressed as kilograms above or below that predicted from stature growth. The residuals of weight on height were determined for parental and newborn data to enable the simultaneous incorporation in the statistical models of both a measure of stature and a measure of weight. To account for potential nonlinear associations, stature variables were modeled as either a linear or quadratic term, depending on which was more strongly associated with weight or weight gain.

Parental and early-life factors associated with postnatal weight gain were determined by multivariable linear regression adjusting for age at 18-month visit, gender, maternal education, and study randomization group. The selection of variables incorporated in the model was hypothesis driven. Associations of postnatal weight gain with end points at age 8 years were determined by Pearson’s correlation and multivariable linear regression for continuous variables and by logistic regression for categorical variables. Multivariable models were adjusted for age at the 8-year visit, gender, maternal education, and study randomization group. Additional adjustment for paternal education, maternal and paternal employment, and maternal and paternal country of birth did not alter our findings with regard to adiposity, cardiovascular risk factors, and carotid IMT at 8 years of age (results not shown). One individual had an outlying BMI z score of −4.1 at 8 years. The exclusion of this participant did not alter the results (data not shown).

RESULTS
Participants
Characteristics of the 395 children with data on weight gain and carotid IMT, and the subset of 319 of these participants with blood samples at 8 years, are shown in Table 1. The SD for height-adjusted weight gain from birth to 18 months of age was 1.1 kg, and participants gained, on average, 8.0 (SD: 1.3) kg during the first 18 months of postnatal life.

Factors Associated With Weight Gain Between 0 and 18 Months
Variables significantly associated with height-adjusted weight gain from 0 to 18 months were male gender ($r = 0.227$, $P < .001$), gestational duration ($r = −0.100$, $P = .05$), birth weight ($r = 0.136$, $P = .007$), birth length ($r = 0.317$, $P < .001$), Ponderal index at birth ($r = −0.203$, $P < .001$), breastfeeding for at least 6 months ($r = −0.221$, $P < .001$), maternal height ($r = 0.125$, $P = .01$), maternal weight ($r = 0.113$, $P = .03$).
TABLE 1 Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>199 (50)</td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>39.6 (1.3)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.49 (0.48)</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>51.0 (2.4)</td>
</tr>
<tr>
<td>Any breastfeeding, %</td>
<td>364 (92)</td>
</tr>
<tr>
<td>Breastfeeding at 6 months, %</td>
<td>165 (42)</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td>29.5 (5.0)</td>
</tr>
<tr>
<td>Maternal parity, previous live births</td>
<td>1.1 (1.1)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy, %</td>
<td>90 (23)</td>
</tr>
<tr>
<td>Maternal height, m</td>
<td>1.62 (0.07)</td>
</tr>
<tr>
<td>Maternal BMI, kg/m²</td>
<td>28.4 (7.2)</td>
</tr>
<tr>
<td>Paternal BMI, kg/m²</td>
<td>28.5 (5.0)</td>
</tr>
<tr>
<td>Paternal height, m</td>
<td>1.77 (0.07)</td>
</tr>
<tr>
<td>Paternal weight, kg</td>
<td>9.0 (1.3)</td>
</tr>
<tr>
<td>Age at 8-year visit, y</td>
<td>8.0 (0.1)</td>
</tr>
<tr>
<td>Weight at 8 years, kg</td>
<td>29.1 (6.7)</td>
</tr>
<tr>
<td>Height at 8 years, m</td>
<td>1.28 (0.06)</td>
</tr>
<tr>
<td>BMI z score at 8 years</td>
<td>0.51 (1.02)</td>
</tr>
<tr>
<td>Overweight at 8 years, %</td>
<td>65 (16)</td>
</tr>
<tr>
<td>Obese at 8 years, %</td>
<td>55 (14)</td>
</tr>
<tr>
<td>Waist-to-height ratio at 8 years</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td>Excess central adiposity at 8 years, %</td>
<td>74 (19)</td>
</tr>
<tr>
<td>SBP at 8 years, mm Hg</td>
<td>100.3 (6.8)</td>
</tr>
<tr>
<td>DBP at 8 years, mm Hg</td>
<td>59.1 (5.5)</td>
</tr>
<tr>
<td>Non-HDL-C at 8 years, mmol/L</td>
<td>2.95 (0.70)</td>
</tr>
<tr>
<td>Non-HDL-C at 8 years, mg/dl</td>
<td>114 (27)</td>
</tr>
<tr>
<td>HDL-C at 8 years, mmol/L</td>
<td>1.46 (0.37)</td>
</tr>
<tr>
<td>HDL-C at 8 years, mg/dl</td>
<td>56 (14)</td>
</tr>
<tr>
<td>hsCRP at 8 years, mg/dl</td>
<td>0.52 (0.09)</td>
</tr>
<tr>
<td>Maximum carotid IMT at 8 years, mm</td>
<td>0.77 (0.05)</td>
</tr>
</tbody>
</table>

Data are presented as means (SD) for continuous variables and n (%) for dichotomous variables, except for hsCRP which was log-transformed for analysis and presented as the geometric mean (interquartile range). A = 395, except for maternal height (n = 378), paternal BMI (n = 378), paternal height (n = 361), paternal BMI (n = 360), non-HDL-C (n = 308), HDL-C (n = 308), and hsCRP (n = 517).

were associated with height-adjusted weight gain and change in weight-for-height z score (Table 2).

Weight Gain Between 0 and 18 Months and Adiposity at 8 Years

Weight gain, height-adjusted weight gain, and change in weight-for-height z score from 0 to 18 months were strongly associated with measures of adiposity at 8 years of age, including BMI z score (Table 3, Fig 1, Supplemental Figs 2–4) and waist-to-height ratio (0.014 [95% confidence interval (CI): 0.010 to 0.019] per kg height-adjusted weight gain, P < .001). This association was independent of gestational age, birth length, birth weight, breastfeeding, and paternal adiposity (Supplemental Table 5), and represents a 2.7 [95% CI: 2.2 to 3.3] kg greater weight at age 8 years per kilogram of height-adjusted weight gain from 0 to 18 months, and a significantly increased odds of overweight and obesity (healthy weight odds ratio [OR] = 1.00 [referent], overweight at 8 years OR = 1.67 [95% CI: 1.26 to 2.20] per kg height-adjusted weight gain, obese at 8 years OR = 2.07 [95% CI: 1.53 to 2.79] per kg height-adjusted weight gain), and excess central adiposity at 8 years (OR = 1.54 [95% CI: 1.20 to 1.98] per kg height-adjusted weight gain).

Weight Gain Between 0 and 18 Months and Cardiovascular Risk Factors at 8 Years

Weight gain, height-adjusted weight gain, and change in weight-for-height z score from 0 to 18 months were associated with blood pressure at age 8 years (SBP: Table 3, Fig 1, Supplemental Figs 2–4; DBP: 0.81 mm Hg [95% CI: 0.28 to 1.38] per kg height-adjusted weight gain, P = .003) and hsCRP (0.17 mg/dL [95% CI: 0.05 to 0.28], P = .006 per 100% increase in height-adjusted weight gain). These associations were independent of gestational age, birth length, birth weight, breastfeeding, and paternal adiposity (SBP: Supplemental Table 5; hsCRP: 0.14 mg/dL [95% CI: 0.01 to 0.28] per 100% increase in height-adjusted weight gain, P = .04); however, they were attenuated by adjustment for BMI z score at age 8 years (SBP: 0.07 mm Hg [95% CI: −0.59 to 0.73] per kg height-adjusted weight gain, P = .83; hsCRP: −0.02 mg/dL [95% CI: −0.14 to 0.10] per 100% increase in height-adjusted weight gain, P = .71).

No measure of weight gain between 0 and 18 months was associated with HDL-C or non–HDL-C concentrations at 8 years of age (HDL-C: −0.01 mmol/L [95% CI: −0.06 to 0.03] per kg height-adjusted weight gain, P = .49; non–HDL-C: 0.07 mmol/L [95% CI: −0.01 to 0.14] per kg height-adjusted weight gain, P = .09).

Weight Gain Between 0 and 18 Months and Carotid IMT at 8 Years

Weight gain, height-adjusted weight gain, and change in weight-for-height z score from 0 to 18 months were strongly associated with carotid IMT at 8 years of age (Table 3, Fig 1, Supplemental Figs 2–4), independent of gestational age, birth length, birth weight, breastfeeding, and paternal adiposity (Supplemental Table 5), BMI z score (0.01 mm [95% CI: 0.002 to 0.018] per kg height-adjusted weight gain, P = .02) and waist-to-height ratio at 8 years of age (0.012 mm [95% CI: 0.004 to 0.020] per kg height-adjusted weight gain, P = .002). These data suggest an independent effect of early weight gain on arterial wall thickening in later childhood.

DISCUSSION

In this article, we revealed that postnatal weight gain, from birth to 18 months of age, is associated with overweight and obesity, central adiposity, higher SBP, higher systemic inflammation, and greater arterial wall thickness later in childhood. Independent predictors of early weight gain included shorter...
gestation, birth length, and failure to breastfeed until 6 months of age.

We found that the effect of early weight gain was amplified by later childhood, with weight at 8 years being 2.1 to 3.3 kg higher for every 1 kg of early weight gain from birth to 18 months beyond that expected from stature growth. With regard to the magnitude of the observed association of postnatal weight gain with later subclinical atherosclerosis, a 2-kg difference in height-adjusted postnatal weight gain (<2 SDs) was associated with a 0.024-mm difference in carotid IMT, similar to that associated with type 1 diabetes in children of a similar age.22-24

These data suggest that weight gain during the first 18 months after birth may be an important determinant of future vascular health.

Growth during other critical periods of early life is a risk factor for adult cardiovascular disease. The most established of these critical periods is the prenatal period, with a large and consistent body of literature indicating that birth weight is inversely associated with cardiovascular disease risk in adulthood.25 Consistent with this risk possibly being mediated via atherosclerotic pathways, we have previously reported that people born with impaired fetal growth have increased subclinical atherosclerosis from early childhood through early adulthood.20,26 Evidence concerning growth during the early postnatal period is less well established. Excessive early weight gain may be associated with later childhood obesity and obesity-related risk factors,27 with weight gain from birth to 1 year of age and birth to 2 years of age both being important antecedents of subsequent body size later in childhood.4 Childhood obesity is, in turn, predictive of subclinical atherosclerosis in adulthood.28

With regard to an association between early weight gain and later cardiovascular risk factors, 1 previous study in individuals born at term found a direct association of SBP in young adulthood with change in weight from birth to 5 months of age, and from 1 year 9 months of age to 5 years of age.29 Change in height during the same periods was more strongly associated with later blood pressure in the same study, suggesting that stature growth, as opposed to adiposity, may have been driving the associations with weight change.

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**TABLE 2 Multivariable Determinants of Weight Gain Between 0 and 18 Months**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight Gain (kg) (n = 348)</th>
<th>Height-Adjusted Weight Gain (kg) (n = 348)</th>
<th>Change in Weight-for-Height z Score (n = 347)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta ) (95% CI)</td>
<td>( \beta ) (95% CI)</td>
<td>( \beta ) (95% CI)</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.685 (-0.938 to -0.452)</td>
<td>-0.411 (-0.614 to -0.207)</td>
<td>-0.163 (-0.389 to 0.063)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>-0.187 (-0.290 to -0.085)</td>
<td>-0.121 (-0.206 to -0.055)</td>
<td>0.062 (-0.225 to -0.033)</td>
</tr>
<tr>
<td>Birth weight* (kg)</td>
<td>0.160 (-0.181 to 0.502)</td>
<td>-0.136 (-0.421 to 0.150)</td>
<td>0.351 (-1.97 to -1.66)</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>0.067 (0.011 to 0.123)</td>
<td>0.156 (0.110 to 0.202)</td>
<td>0.001 (0.389 to 0.440)</td>
</tr>
<tr>
<td>Breastfeeding at 6 months</td>
<td>-0.588 (-0.852 to -0.344)</td>
<td>-0.498 (-0.711 to -0.286)</td>
<td>-0.001 (-0.753 to -0.283)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>0.102 (-0.208 to 0.415)</td>
<td>0.116 (-0.144 to 0.575)</td>
<td>0.103 (-0.187 to 0.394)</td>
</tr>
<tr>
<td>Maternal height (m)</td>
<td>1.84 (0.31 to 3.39)</td>
<td>0.82 (-0.81 to 2.45)</td>
<td>0.79 (-1.02 to 2.58)</td>
</tr>
<tr>
<td>Maternal adiposity* (kg)</td>
<td>0.000 (-0.007 to 0.007)</td>
<td>-0.000 (-0.006 to 0.005)</td>
<td>-0.000 (-0.006 to 0.006)</td>
</tr>
<tr>
<td>Paternal height (m)</td>
<td>1.96 (0.21 to 3.71)</td>
<td>0.06 (-1.40 to 1.53)</td>
<td>0.329 (-1.292 to 1.949)</td>
</tr>
<tr>
<td>Paternal adiposity* (kg)</td>
<td>0.007 (-0.001 to 0.015)</td>
<td>0.006 (-0.000 to 0.013)</td>
<td>0.006 (0.001 to 0.015)</td>
</tr>
</tbody>
</table>

Values are unstandardized \( \beta \)-regression coefficients (95% CI) from a single multivariable model incorporating all variables and adjusted for age at 18-month visit, maternal education, and randomization group. Results shown are increase in weight gain, height-adjusted weight gain, or change in weight-for-height z-score per unit increase in the independent variable.

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**TABLE 3 Multivariable Model of Height-Adjusted Weight Gain From 0 to 18 Months and Cardiovascular Risk Factors at 8 Years of Age**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI ( z ) score</th>
<th>( \beta ) (95% CI)</th>
<th>SBP (mm Hg)</th>
<th>( \beta ) (95% CI)</th>
<th>Carotid IMT (mm)</th>
<th>( \beta ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.37 (-0.29 to 1.04)</td>
<td>0.27</td>
<td>3.5 (-1.6 to 8.1)</td>
<td>0.18</td>
<td>0.00 (-0.06 to 0.05)</td>
<td>0.91</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.13 (-0.06 to 0.32)</td>
<td>0.19</td>
<td>1.2 (-0.2 to 2.6)</td>
<td>0.08</td>
<td>0.00 (-0.02 to 0.01)</td>
<td>0.71</td>
</tr>
<tr>
<td>Randomization</td>
<td>0.03 (-0.16 to 0.21)</td>
<td>0.79</td>
<td>0.2 (-1.2 to 1.5)</td>
<td>0.78</td>
<td>0.01 (-0.01 to 0.02)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dust mite reduction</td>
<td>-0.08 (-0.27 to 0.10)</td>
<td>0.38</td>
<td>0.3 (-1.0 to 1.7)</td>
<td>0.61</td>
<td>0.00 (-0.01 to 0.02)</td>
<td>0.87</td>
</tr>
<tr>
<td>Maternal education</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>( \leq 10 ) years of school</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>11–12 years of school</td>
<td>-0.02 (-0.22 to 0.21)</td>
<td>0.95</td>
<td>0.7 (-3.6 to 5.0)</td>
<td>0.74</td>
<td>-0.02 (-0.05 to 0.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Tertiary education</td>
<td>-0.01 (-0.60 to 0.58)</td>
<td>0.01</td>
<td>1.24 (0.59 to 1.88)</td>
<td>&lt;0.001</td>
<td>0.012 (0.004 to 0.019)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Height-adjusted weight gain from 0 to 18 mo (kg)</td>
<td>0.416 (0.327 to 0.506)</td>
<td>&lt;0.01</td>
<td>1.24 (0.59 to 1.88)</td>
<td>&lt;0.001</td>
<td>0.012 (0.004 to 0.019)</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Values are unstandardized \( \beta \)-regression coefficients (95% CI) from a single multivariable model incorporating all variables; \( N = 395 \). Results shown are increase in BMI \( z \) score, SBP, or carotid IMT per kilogram increase in height-adjusted weight gain from 0 to 18 months.
Of particular pertinence to early weight gain from birth to 18 months of age, the recent National Heart, Lung, and Blood Institute’s Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommend that fat intake from ages 12 to 24 months should be limited to 30% of total calories and saturated fat to 7% to 10% of calories, supported if required by the introduction of reduced fat milk, and that sugar-sweetened beverages should be avoided from ages 6 to 12 months and avoided or limited from ages 12 to 24 months. When taken in the context of our results, these recommendations may result in improved cardiovascular risk markers, including reduced obesity, in later childhood.

Limitations of this study include the use of carotid IMT as a measure of vascular health. Intima-media thickening is an established measure of “subclinical atherosclerosis” in adults; however, the relative contribution of fatty streaks, for example, to intima-media thickening in prepubertal children is less certain. Similarly, although hsCRP concentrations predict cardiovascular event rates in adults with or without coronary disease, the prognostic relevance of hsCRP in children is not established. In addition, although these children were community-based, participants were considered “at risk” of developing asthma and had been involved in a randomized trial related to the prevention of asthma until age 5 years. Nonetheless, participants had an anthropometric and cardiovascular risk profile similar to that from an unselected community-based population of a similar age from the same geographical area. We cannot exclude potential residual confounding by socioeconomic status; however, additional adjustment for paternal education, maternal and paternal employment, and maternal and paternal country of birth did not materially alter our results. Finally, we analyzed a sample of 395 subjects from the 616 originally randomized subjects. Many of the participants who were lost to follow-up were lost within the first 18 months of the trial (n = 62) and in the 3-year period between the conclusion of...
the randomized trial at age 5 years and the first posttrial visit at age 8 years (n = 56). An additional 40 participants attended the 8-year visit but did not consent to the vascular testing. Nonetheless, the participants included in this analysis were largely similar to those who did not participate, with the exception of having older mothers with a higher prevalence of tertiary education, and a higher prevalence of breastfeeding at 6 months of age.

CONCLUSIONS
Early postnatal weight gain from birth to age 18 months potentially affects later body size and arterial development, being independently associated with childhood overweight and obesity, excess central adiposity, and greater arterial wall thickness. We have identified, for example, that breastfeeding is a potentially modifiable factor associated with significantly less early-life weight gain. Future studies could assess whether reducing such early-life weight gain might be associated with improved cardiovascular risk profiles in later life.

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