ORIGINAL RESEARCH

Birth Weight, Postnatal Weight Gain, and Childhood Adiposity in Relation to Lipid Profile and Blood Pressure During Early Adolescence

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***Background*—**Different pathways likely underlie the association between early weight gain and cardiovascular disease risk. We examined whether birth weight for length relationship and weight gain up to 2 years of age are associated with lipid profiles and blood pressure (BP) in early adolescence and determined whether childhood adiposity mediates these associations.

***Methods and Results*—**Data from QUALITY (Quebec Adipose and Lifestyle Investigation in Youth), a cohort of white children with parental history of obesity, were analyzed (n=395). Sex-specific weight for length *z* scores from birth to 2 years were computed. Rate of postnatal weight gain was estimated using individual slopes of weight for length *z*-score measurements. Percentage of body fat was measured at 8 to 10 years. Fasting lipids and BP were measured at 10 to 12 years. Using path analysis, we found indirect effects of postnatal weight gain, through childhood adiposity, on all outcomes: Rate of postnatal weight for length gain was positively associated with childhood adiposity, which in turn was associated with unfavorable lipid and BP levels in early adolescence. In contrast, small beneficial direct effects on diastolic BP *z* scores, independent of weight at other time points, were found for birth weight for length (β=−0.05, 95% CI, −0.09 to −0.002) and for postnatal weight gain (β=−0.02, 95% CI, −0.03 to −0.002).

***Conclusions*—**Among children with at least 1 obese parent, faster postnatal weight gain leads to cardiovascular risk factors in early adolescence through its effect on childhood adiposity. Although heavier newborns may have lower BP in early adolescence, this protective direct effect could be offset by a deleterious indirect effect linking birth weight to later adiposity. **(*J Am Heart Assoc*. 2017;6:e006302. DOI: 10.1161/JAHA.117.006302.)**

Key Words: birth weight • blood pressure • lipid profile • obesity • postnatal weight gain

Cardiovascular diseases are leading causes of death worldwide,[1] and associated morbidities result in major economic burdens.[2] There is mounting evidence that cardiovascular diseases originate early in life[3] and that associated risk factors in childhood are predictive of later diseases.[4,5] Among Canadian children and youth, it is estimated that 4% have high or borderline blood pressure (BP)[6] and 35% have unfavorable levels of total cholesterol.[7] Timely primary prevention is crucial, yet our understanding of the earliest predictors of cardiovascular risk factors remains incomplete.

Growth patterns throughout infancy, in particular small birth size for gestational age and rapid postnatal weight gain have been associated with cardiovascular risk factors in both children and young adults, including abnormal lipid levels and elevated BP.[8–13] Similarly, being born large for gestational age has been linked with adverse cardiovascular consequences.[10,14,15] However, in studies carried out on representative population-based samples, mixed findings have been reported for associations of birth weight and postnatal weight gain with lipid profiles[16–19] and with BP[16,20–23] in children. Substantial heterogeneity between studies, namely, with regard to the inclusion of participants with birth weights at the lower and upper extremes of the distribution, may in part explain contrasting findings. In addition, most of the literature has focused on birth weight and postnatal weight gain without accounting for growth in length. Weight for length during infancy may be a better predictor of later overweight/obese status than weight alone.[24,25]

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Accompanying Tables S1 through S7 are available at http://jaha.ahajournals.org/content/6/8/e006302/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Children born at term who had at least 1 obese parent and who experienced faster weight gain in the first 2 years of life had higher adiposity at ages 8 to 10 years, which in turn predicted worse fasting lipid and blood pressure levels 2 years later.
- Our findings do not support direct associations of birth weight for length and postnatal weight gain up to 2 years of age on fasting lipid or blood pressure levels, independent of childhood adiposity, with the exception of diastolic blood pressure.

What Are the Clinical Implications?

- Promoting healthy patterns of weight gain throughout the life course, including prenatally, during the first 2 years of life and throughout childhood may reduce the occurrence of obesity and its deleterious consequences for cardiovascular health.

Childhood weight status may be an important mediator in associations between early weight gain and cardiovascular risk factors.[26] Birth weight and rate of postnatal weight gain are positively associated with adiposity in childhood,[27,28] and adiposity is an important predictor of cardiovascular risk factors.[29] In analyses estimating direct effects of birth weight and postnatal weight gain on cardiovascular risk factors, it has been common practice to statistically adjust for adiposity measured contemporaneously with cardiovascular risk factors[16–18]; however, collider-stratification bias may result in biased direct effect estimates.[30] To better understand prospective associations among early weigh gain, childhood adiposity, and cardiovascular risk factors in early adolescence, we examined the associations between birth weight for length and rate of postnatal gain in weight for length up to 2 years of age with lipid profiles and BP at ages 10 to 12 years, and we assessed whether these associations were mediated by childhood adiposity.

Methods

Participants were drawn from the QUALITY (Quebec Adipose and Lifestyle Investigation in Youth) cohort, an ongoing longitudinal study of the natural history of obesity and cardiovascular risk factors in white youth. Children were recruited through elementary schools located within 3 major urban centers in Quebec, Canada. Eligibility criteria required participants to be white, aged 8 to 10 years at recruitment, with both biological parents available to participate in baseline data collection and at least 1 parent being obese (ie, body mass index ≥30 and/or waist circumference >102 cm in men and >88 cm in women). At baseline, 630 families participated in a clinic visit during which biological and physiological measurements were obtained, and questionnaires were completed between 2005 and 2008. A similar assessment was conducted 2 years later, when participants were aged 10 to 12 years, between 2008 and 2011 (n=564). Written informed consent was obtained from parents, and children provided assent. The ethics review boards of the CHU Sainte Justine and the Quebec Heart and Lung Institute approved the study. A detailed description of the study design and data collection methods is available.[31]

For the current analysis, we used a subsample of QUALITY participants (n=395) who were born at term (ie, 37 to <42 weeks of gestation), who had complete anthropometric data up to 2 years of age, and who completed a follow-up visit at age 10 to 12 years. Participants included in the analysis differed from those excluded in that they had slightly higher triglycerides (P=0.049), higher diastolic BP (P=0.021), and lower likelihood of having been exposed to tobacco in utero (P=0.010; Table S1).

Measures at Birth and Up to 2 Years

Health booklets are issued to all Quebec parents of newborn children; growth and other health-related information is subsequently entered by health professionals (nurses or physicians) during routine medical visits. From these booklets, birth weight and length, gestational age, and measurements of weight and length collected at different times up to 24 months of age were obtained. For the current analysis, participants were required to have a minimum of 3 measurement times over the first 24 months of life (ie, at birth, at least once between 1 and 12 months, and at least once between 12.1 and 24 months; median: 6 entries [range: 3–10 entries]). Measures of weight and length were transformed to sex-specific weight-for-length z scores using the World Health Organization growth standards.[32] Individual slopes (rate of increase or decrease) for weight for length z scores from birth to 2 years were used to estimate postnatal weight gain. To do so, simple linear regressions were fitted to measurements of each participant, with age in months as an independent variable and weight-for-length z score as a dependent variable. The slope thus represents the estimated rate of postnatal growth in weight-for-length z score per month during the first 2 years of life. To facilitate its interpretation, we rescaled the variable such that 1 U of the slope variable corresponds to a change of z=0.02 per month, which is equivalent to ≈0.5 SD (z=0.48) over a 24-month period. The latter also corresponds to biologically plausible growth in weight for length.

Size at birth for gestational age was based on Canadian reference values for gestational age and sex-specific

percentile: small for gestational age was defined as a birth weight <10th percentile, large size for gestational age as a birth weight >90th percentile, and appropriate for gestational age (AGA) otherwise.[33] Parent-completed questionnaires assessed history of gestational diabetes mellitus, smoking, and hypertension during the pregnancy of the child participating in the study and whether the child was breastfed (never, <3 months, 3–6 months, or >6 months).

Measures in Childhood (8–10 Years)

Body composition was measured by dual-energy x-ray absorptiometry when participants were aged 8 to 10 years. Childhood adiposity was estimated using the percentage of body fat calculated as total fat mass/total body mass × 100. Parental educational attainment was assessed by questionnaire (2 parents with secondary school or less versus at least 1 parent with a technical/vocational/trade or university degree). Maternal body mass index was computed from weight and height measured using standard protocols when children were aged 8 to 10 years.[31] Pubertal development stage was assessed by trained nurses using the 5-stage Tanner scales[34,35] and was dichotomized as prepubertal (Tanner 1) versus puberty initiated (Tanner >1).

Measures in Early Adolescence (10–12 Years)

Blood samples were obtained by venipuncture after a 10-hour overnight fast. Blood samples were centrifuged, aliquoted, and stored at −80°C until analyzed. Lipid profiles (total cholesterol, high density lipoprotein [HDL] cholesterol, and triglycerides) were measured on a Synchron LX20 analyzer, with Beckman Instruments reagents, by the Department of Clinical Biochemistry at CHU Sainte-Justine, according to the recommendations of the International Federation of Clinical Chemistry. Low-density lipoprotein cholesterol was calculated based on the Friedewald equation.[36] BP was measured on the right arm, with the child in a sitting position and at rest for at least 5 minutes, using an oscillometric instrument (Dinamap XL Vital Signs Monitors, model 9300; Johnson & Johnson Medical Inc). Five consecutive measures were obtained at 1-minute intervals, and the average of the last 3 (of 5) measures of systolic and diastolic BP was used in the analyses. These were then transformed to age-, sex- and height-specific *z* scores.[37] Last, pubertal development was assessed at age 8 to 10 years.

Statistical Analyses

Means and standard deviations or proportions were used to describe participants. Multivariable linear regression analyses were used to examine the association of weight for length at birth and rate of postnatal weight gain with each outcome. Variables from the lipid profile were transformed (100 × natural logarithm of variable) to normalize their distribution. The β coefficients for lipid variables thus represent the percentage of change in the dependent variable for a 1-U increase in the independent variable.[38] In addition to birth weight for length and postnatal weight gain, all models included sex; age; parental education; maternal history of gestational diabetes mellitus, smoking, or hypertension during pregnancy; gestational age; and breastfeeding duration. Pubertal development is likely not a confounder and could be in the causal pathway for associations of interest (eg, if children who grow more rapidly experience earlier puberty). However, given that puberty was not associated with birth weight or postnatal weight gain in our data and that its inclusion in models did not change the magnitude of β coefficients associated with early weight gain, models were not adjusted for pubertal development. Regression models were also adjusted for the suspected mediator (ie, childhood percentage of body fat mass) to estimate direct effects of birth weight for length and subsequent postnatal weight gain on cardiovascular risk factors. The linearity assumption for associations between independent variables and outcomes was tested using nonparametric smoothing splines and was found not to be violated. Indirect effects of birth weight for length and of postnatal weight gain on cardiovascular risk factors, via childhood adiposity, were estimated using path analysis (SAS proc calis; Figure).

In sensitivity analyses, we tested the presence of interactions between sex and birth weight for length and between sex and postnatal weight gain using interaction terms included one at a time in covariate-adjusted models. Statistically significant interactions were found for triglycerides and for HDL cholesterol; sex-stratified analyses for these 2 outcomes are presented in Tables S3–S4. Last, given that mechanisms linking early growth and later cardiovascular risk factors may be different for participants born with extreme birth weights, we repeated all analyses in a sample restricted to children born AGA (n=318), for which results are also presented in Tables S5–S7. All analyses were conducted with SAS version 9.4.

Results

Participants included in this analysis were born between August 1994 and September 2000. Mean birth weight and birth length were 3.6 kg (SD: 0.5) and 51.4 cm (SD: 2.3). The correlation between birth weight for length and postnatal weight gain was −0.54. At 8 to 10 years of age, 54% of children were normal weight, whereas 22% were overweight and 24% were obese. Lipid profiles and BP were measured when children were, on average, aged 11.6 years (SD: 0.9). Characteristics of participants are shown in Table 1.

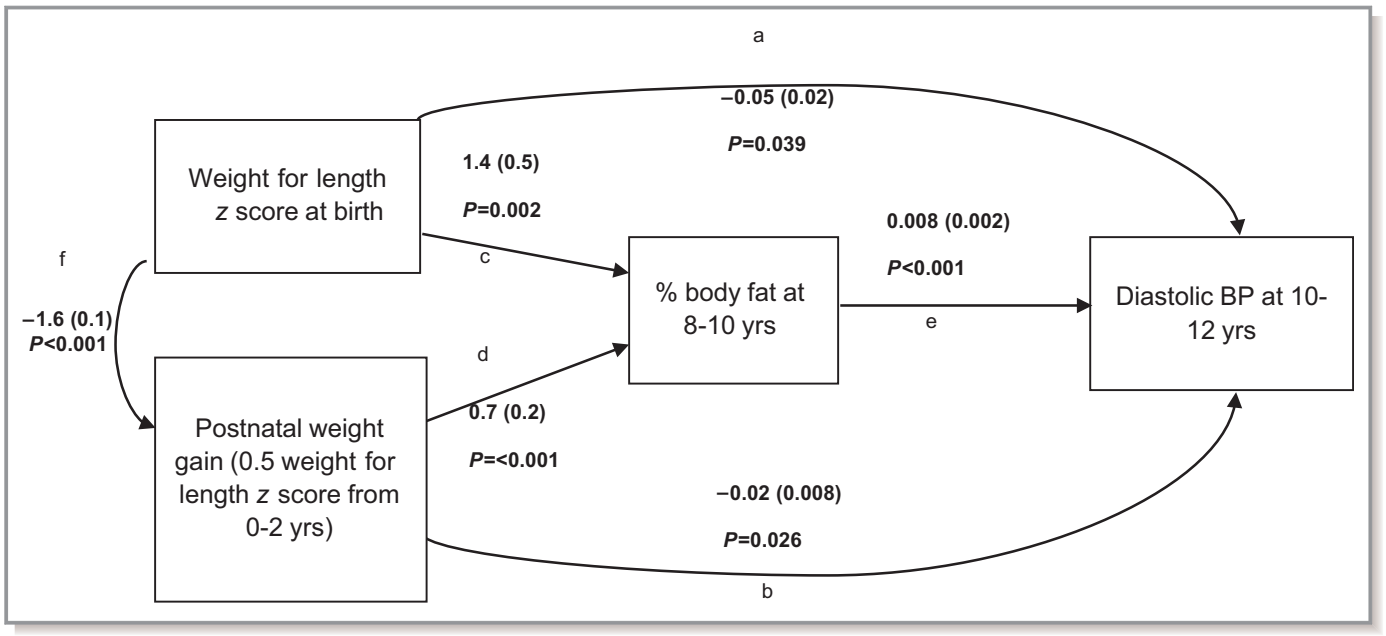

Figure. Path diagrams showing relationships between birth weight for length *z* score, postnatal weight gain, adiposity at 8 to 10 years of age, and diastolic blood pressure (BP) at 10 to 12 years of age among 395 children from the QUALITY cohort. The β coefficients (standard errors) and *P* values are presented for diastolic BP. All associations are adjusted for child's age, sex, parental education, gestational age, breastfeeding, and in utero exposure to gestational diabetes mellitus, maternal hypertension, and maternal smoking. The direct effect of birth weight for length (not mediated by adiposity) on the outcome corresponds to coefficient (a). The direct effect of postnatal weight gain (not mediated by adiposity) on the outcome corresponds to coefficient (b). The indirect effect of birth weight for length on the outcome (mediated by postnatal growth and by adiposity) corresponds to (f×b)+(f×d×e)+(c×e). The indirect effect of postnatal weight gain on the outcome (mediated by adiposity) corresponds to (d×e).

Correlations between measurements at ages 8 to 10 and 10 to 12 years for adiposity, lipid profiles, and BP are shown in Table S2.

Before adding childhood adiposity to models for the lipid profile (Table 2), postnatal weight gain was associated with HDL cholesterol: Every additional *z*=0.5 in weight for length over the first 2 years of life was associated with a 0.7% decrease in HDL cholesterol at 10 to 12 years (95% confidence interval, −1.4 to −0.007). In sex-specific analysis, this association was found only in boys (Table S3). Following adjustment for adiposity, neither birth weight for length nor postnatal weight gain had direct effects on lipid levels. Childhood adiposity was strongly associated with lipid levels in early adolescence.

Prior to adjustment for childhood adiposity, no associations were found between birth weight for length or postnatal weight gain and BP (Table 3). However, adjusting for adiposity resulted in small negative associations between birth weight for length *z* score and diastolic BP (β=−0.05, 95% confidence interval, −0.09 to −0.002) and between postnatal weight gain and diastolic BP (β=−0.02, 95% confidence interval, −0.03 to −0.002). These correspond to decreases in diastolic BP of ≈0.6 mm Hg for every additional weight for length *z* score at birth and 0.2 mm Hg for every additional *z*=0.5 increase in weight for length over the first 2 years of life.

Path analysis showed indirect effects of postnatal weight gain on all outcomes: Rate of postnatal weight gain was positively associated with childhood adiposity, with the latter predicting unfavorable lipid and BP levels in early adolescence (Table 4 and Figure). For triglycerides and HDL cholesterol, these indirect effects were slightly stronger in girls compared with boys but still present in both sexes (Table S4). Birth weight for length had an indirect effect (ie, mediated by postnatal weight gain and childhood adiposity) on diastolic BP only. Indirect effects of birth weight for length and postnatal weight gain on diastolic BP were in opposite directions of respective direct effects.

Overall, results were similar when restricting the sample to children born AGA (Tables S5–S7). However, in the restricted sample, after adjustment for childhood adiposity, postnatal weight gain was no longer associated with diastolic BP.

Discussion

Our study elucidates the distinct links among birth weight adjusted for length, postnatal weight gain during the first 2 years of life, childhood adiposity, and cardiovascular risk factors in young adolescents who were born at term and who have at least 1 obese parent. With the exception of diastolic BP, we found no evidence of direct effects of early growth (at

Table 1. Characteristics of Study Population for 395 Children of the QUALITY Cohort, Quebec, Canada, 2005–2011

Characteristics	All (n=395)	Boys (n=225)	Girls (n=170)
Birth to 2 years of age			
Birth weight, kg, mean, SD	3.6 (0.5)	3.6 (0.5)	3.5 (0.5)
Birth length, cm, mean, SD	51.4 (2.3)	51.8 (2.2)	51.0 (2.2)
Birth weight for length *z* score, mean, SD	−0.3 (1.3)	−0.3 (1.3)	−0.3 (1.3)
Postnatal weight gain*, *z* score per month, mean, SD	0.06 (0.08)	0.06 (0.08)	0.06 (0.07)
Gestational age, mean, SD	39.6 (1.1)	39.5 (1.1)	39.6 (1.1)
Size at birth for gestational age, % (n)			
SGA	6.6 (26)	5.3 (12)	8.2 (14)
AGA	80.5 (318)	81.3 (183)	79.4 (135)
LGA	12.9 (51)	13.3 (30)	12.4 (21)
Breastfeeding duration, % (n)			
Never breastfed	19.5 (76)	20.6 (45)	18.2 (31)
Breastfed <3 mo	26.7 (104)	28.8 (63)	24.1 (41)
Breastfed 3–6 mo	24.4 (95)	23.3 (51)	25.9 (44)
Breastfed >6 mo	29.3 (114)	27.4 (60)	31.8 (54)
In utero exposure to gestational diabetes mellitus, % (n)	17.2 (68)	20.4 (46)	12.9 (22)
In utero exposure to maternal hypertension, % (n)	9.9 (39)	11.6 (26)	7.7 (13)
In utero exposure to maternal smoking, % (n)	12.4 (49)	13.4 (30)	11.2 (19)
Childhood (8–10 y)			
Total body fat mass, %, mean, SD	25.9 (10.7)	23.6 (10.7)	28.9 (9.9)
BMI category†, % (n)			
Normal weight	54.2 (214)	52.9 (119)	55.9 (95)
Overweight	21.5 (85)	22.2 (50)	20.6 (35)
Obese	24.3 (96)	24.9 (56)	23.5 (40)
Puberty (Tanner stage >1), % (n)	21.3 (84)	8.9 (20)	37.7 (64)
Early adolescence (10–12 y)			
Child's age, y, mean, SD	11.6 (0.9)	11.7 (0.9)	11.6 (0.9)
Puberty (Tanner stage >1), % (n)	66.8 (264)	52.4 (118)	85.9 (146)
Lipids			
Total cholesterol, mmol/L, mean, SD	3.7 (0.7)	3.8 (0.6)	3.7 (0.7)
LDL cholesterol, mmol/L, mean, SD	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)
HDL cholesterol, mmol/L, mean, SD	1.2 (0.2)	1.2 (0.3)	1.1 (0.2)
Triglycerides, mmol/L, mean, SD	0.8 (0.4)	0.8 (0.5)	0.8 (0.4)
Blood pressure			
Systolic, mm Hg, mean, SD	97.7 (8.9)	98.6 (8.6)	96.5 (9.1)
Diastolic, mm Hg, mean, SD	50.7 (5.3)	50.7 (5.2)	50.8 (5.5)
Parent characteristics			
Parental education, % (n)			
2 parents with high school degree or less	6.6 (26)	4.9 (11)	8.8 (15)
1 or 2 parents with technical or university degree	93.4 (369)	95.1 (214)	91.2 (155)
Maternal age at conception of child, y, mean, SD	30.1 (4.6)	30.1 (4.6)	30.0 (4.7)
Maternal BMI, kg/m^2, mean, SD	29.2 (6.5)	29.3 (6.4)	29.0 (6.7)

AGA indicates appropriate birth size for gestational age; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LGA, large birth size for gestational age; QUALITY, Quebec Adipose and Lifestyle Investigation in Youth; SGA, small birth size for gestational age.

*Postnatal weight gain is estimated using the slope for weight for length *z* scores from birth to 24 months of age.

†BMI categories are based on World Health Organization cutoffs for sex- and age-adjusted BMI *z* scores.

Table 2. Associations* of Birth Weight for Length, Postnatal Weight Gain, and Childhood Adiposity With Plasma Lipids Measured at Ages 10–12 Years in 395 Children From the QUALITY Cohort, Quebec, Canada, 2005–2011

	Total Cholesterol		LDL Cholesterol		Triglycerides		HDL Cholesterol	
Model 1: adjusted for covariates								
Birth weight for length *z* score	−0.1	(−1.8 to 1.6)	0.2	(−2.3 to 2.6)	−0.6	(−5.2 to 3.9)	−0.6	(−2.6 to 1.4)
Postnatal weight gain (0.5 weight-for-length z score from 0 to 2 y)	−0.3	(−0.8 to 0.3)	−0.3	(−1.1 to 0.5)	1.4	(−0.2 to 2.9)	−0.7	(−1.4 to −0.007)
Model 2: adjusted for covariates and percentage of body fat								
Birth weight for length *z* score	−0.4	(−2.1 to 1.3)	−0.4	(−2.9 to 2.0)	−3.1	(−7.5 to 1.3)	0.4	(−1.5 to 2.3)
Postnatal weight gain (0.5 weight-for-length *z* score from 0 to 2 y)	−0.4	(−1.0 to 0.2)	−0.6	(−1.5 to 0.2)	0.1	(−1.3 to 1.6)	−0.2	(−0.8 to 0.5)
Percentage of total body fat (at ages 8–10 y)	0.2	(0.03 to 0.4)	0.4	(0.1 to 0.7)	1.7	(1.2 to 2.1)	−0.7	(−0.9 to −0.5)

CI indicates confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QUALITY, Quebec Adipose and Lifestyle Investigation in Youth.
*Birth weight for length and postnatal growth in weight for length are entered simultaneously in model 1, and models are adjusted for child's age, sex, parental education, gestational age, breastfeeding, and in utero exposure to gestational diabetes mellitus, maternal hypertension, and maternal smoking. Model 2 is the same as model 1 but is further adjusted for percentage of total body fat mass. The β coefficients (95% CI) represent the percentage increase or decrease in the outcome for a 1-U increase in the corresponding independent variable.

birth or in the first 2 years of life) on cardiovascular risk factors in early adolescence once childhood adiposity was accounted for. Rate of postnatal weight gain, however, was positively associated with childhood adiposity, which in turn predicted unfavorable lipid and BP outcomes in early adolescence.

The absence of a direct association between birth weight for length and plasma lipid levels is consistent with findings reported elsewhere.[17,39–42] A systematic review by Huxley et al called into question previous reports of associations between birth weight and cholesterol levels, stating that these associations are likely largely a result of publication bias or, if present, that associations are not substantial enough to affect later cardiovascular diseases.[43] We also did not find any direct effect of postnatal weight gain on lipid levels. Some studies that have reported such associations oversampled participants born small for gestational age.[17,44] The physiological response in the lipid profile of faster postnatal weight gain following in utero growth restriction may differ from that of faster postnatal weight gain in largely normal-weight newborns. Our sample included few children born small for gestational age (7%) and thus had insufficient power to test for interactions between size at birth for gestational age and postnatal weight gain. In a study of Chilean adolescent participants with birth weights ≥3 kg, a positive association was reported between faster weight gain from 0 to 3 months and a metabolic syndrome score, including higher triglycerides and lower HDL cholesterol; however, it is not known whether this association is independent of weight in childhood.[45] Weight gain during infancy is likely less predictive of

Table 3. Associations* of Birth Weight for Length, Postnatal Weight Gain, and Childhood Adiposity With BP Measured at Ages 10–12 Years in 395 Children From the QUALITY Cohort, Quebec, Canada, 2005–2011

	Systolic BP		Diastolic BP	
Model 1: adjusted for covariates				
Birth weight for length *z* score	−0.01	(−0.09 to 0.06)	−0.03	(−0.08 to 0.01)
Postnatal weight gain (0.5 weight for length *z* score from 0 to 2 y)	0.01	(−0.01 to 0.04)	−0.01	(−0.03 to 0.004)
Model 2: adjusted for covariates and percentage of body fat				
Birth weight for length *z* score	−0.04	(−0.1 to 0.04)	−0.05	(−0.09 to −0.002)
Postnatal weight gain (0.5 weight for length *z* score from 0 to 2 y)	0.0004	(−0.02 to 0.03)	−0.02	(−0.03 to −0.002)
Percentage of total body fat (at 8–10 y)	0.02	(0.009 to 0.03)	0.008	(0.003 to 0.01)

BP indicates blood pressure; CI, confidence interval; QUALITY, Quebec Adipose and Lifestyle Investigation in Youth.
*Birth weight for length and postnatal growth in weight for length were entered simultaneously in model 1, and models were adjusted for child's age, sex, parental education, gestational age, breastfeeding, and in utero exposure to gestational diabetes mellitus, maternal hypertension and maternal smoking. Model 2 is the same as model 1 but is further adjusted for percentage of total body fat mass. β coefficients (95% CI) for BP *z* scores based on values from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.

Table 4. Coefficients* for Total, Direct, and Indirect Effects (Mediated by Percentage of Body Fat at Ages 8–10 Years) of Birth Weight for Length and Postnatal Weight Gain on Cardiovascular Risk at Ages 10–12 Years Among 395 Children From the QUALITY Cohort, Quebec, Canada, 2005–2011

Effect	Total Cholesterol		LDL Cholesterol		Triglycerides		HDL Cholesterol		Systolic BP, *z* (95% CI)		Diastolic BP, *z* (95% CI)	
Birth weight for length												
Total	0.3	(−1.1 to 1.7)	0.7	(−1.3 to 2.7)	−2.8	(−6.6 to 1.0)	0.5	(−1.2 to 2.1)	−0.03	(−0.09 to 0.03)	−0.01	(−0.05 to 0.02)
Direct	−0.4	(−2.1 to 1.2)	−0.4	(−2.8 to 2.0)	−3.1	(−7.4 to 1.2)	0.4	(−1.5 to 2.3)	−0.04	(−0.1 to 0.03)	−0.05	(−0.09 to −0.002)
Indirect	0.7	(−0.2 to 1.7)	1.1	(−0.3 to 2.5)	0.3	(−2.5 to 3.0)	0.08	(−1.1 to 1.3)	0.004	(−0.04 to 0.05)	0.03	(0.004 to 0.05)
Postnatal weight gain												
Total	−0.3	(−0.8 to 0.3)	−0.3	(−1.1 to 0.5)	1.4	(−0.2 to 2.9)	−0.7	(−1.4 to −0.2)	0.01	(−0.01 to 0.04)	−0.01	(−0.03 to 0.004)
Direct	−0.4	(−1.0 to 0.2)	−0.6	(−1.4 to 0.2)	0.1	(−1.3 to 1.6)	−0.2	(−0.8 to 0.5)	0.0004	(−0.02 to 0.03)	−0.02	(−0.03 to −0.002)
Indirect	0.2	(0.007 to 0.3)	0.3	(0.07–0.5)	1.2	(0.6–1.8)	−0.5	(−0.8 to −0.2)	0.01	(0.005–0.02)	0.006	(0.002–0.01)

BP indicates blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QUALITY, Quebec Adipose and Lifestyle Investigation in Youth.

*Path analysis is applied separately for each outcome variable, models include the 2 main exposure variables (birth weight for length and postnatal weight gain), the suspected mediator (percentage of body fat at ages 8–10 years) and covariates (child's age, sex, parental education, gestational age, breastfeeding, and in utero exposure to gestational diabetes mellitus, maternal hypertension, and maternal smoking). The β coefficients (95% CI) associated with lipid outcomes represent the percentage increase or decrease in the outcome for a 1-U increase in the corresponding independent variable. The β coefficients (95% CI) associated with BP outcomes represent an increase or decrease in BP *z* score for a 1-U increase in the corresponding independent variable.

an adverse lipid profile in comparison to weight gain in subsequent years.[16,40,46]

Our findings are also consistent with the documented inverse association of diastolic BP with birth weight.[26,47] As in other studies, this association became apparent only once childhood adiposity was accounted for.[26,48] Similarly, postnatal weight gain became inversely associated with diastolic BP only after adjustment for childhood adiposity. Collider-stratification bias, which may occur when conditioning on a variable that is in the causal pathway between exposure and outcome (ie, adiposity), has been evoked to explain previously observed direct effects of birth weight on BP[49] and is a possible explanation for our results. Restricting the sample to children born AGA attenuated these direct associations, suggesting that, if present, the beneficial effects of higher birth weight for length and faster postnatal weight gain are driven largely by children whose birth weight was at the extremes of the distribution. More important, the magnitude of the direct effects of birth weight for length and postnatal weight gain on diastolic BP measured in early adolescence was relatively small, suggesting that interventions targeting increased prenatal and postnatal weight gain may have small direct effects on diastolic BP only in early adolescence or even contrary to expected effects via positive associations between early weight gain and childhood adiposity.[50]

Although our study does not support direct effects of birth weight for length and postnatal weight gain on lipid profiles or systolic BP, it distinctly shows that rate of postnatal weight gain progresses into childhood adiposity, which ultimately adversely affects cardiovascular disease risk. Other studies have reported a relationship between postnatal weight gain and BP with associations strengthening for weight gain more proximal to when BP was measured.[51–54] Promoting healthy patterns of weight gain early on could affect cardiovascular disease risk factors through the former's influence on adiposity.

Findings for indirect effects of birth weight for length were less consistent across outcomes: A positive indirect effect was found only for diastolic BP. The indirect effect of birth weight is mediated not only by childhood adiposity but also by postnatal weight gain. In the presence of multiple mediators, the indirect effect coefficient is calculated as the sum of the product of coefficients within each path (Figure). The coefficient for the path linking birth weight for length, childhood adiposity, and cardiovascular risk was systematically positive (negative for HDL cholesterol); however, the coefficient for the path linking birth weight, postnatal growth, childhood adiposity, and cardiovascular risk was systematically negative (positive for HDL cholesterol). When not specifying a path between birth weight for length and postnatal growth (Figure, path f), so as to examine the indirect effect of each variable mediated only by adiposity, we found adverse indirect effects for both higher birth weight and faster postnatal weight gain

on all outcomes (data not shown). This suggests that a higher birth weight could indirectly lead to the development of cardiovascular risk factors in early adolescence, specifically when high birth weight is not followed by slower postnatal weight gain.

Our study includes white children with relatively high standards of living and education from the QUALITY cohort who were born at term. In sensitivity analyses, restricting the sample to participants born AGA yielded similar results, particularly with respect to the detrimental indirect effect of faster postnatal weight gain. To date, few studies have applied statistical methods designed to assess mediation in studies examining early weight gain and cardiovascular risk factors.[21,55] Using path analysis, we were able to estimate direct effects (ie, independent of childhood adiposity) and indirect effects (ie, mediated by postnatal weight gain and childhood adiposity). In addition to our analytical approach, strengths of this study include the availability of repeated measures of weight and length from birth to 2 years of age and adiposity measures from dual-energy x-ray absorptiometry scans obtained 2 years before the measurement of cardiovascular risk factors. Our study has limitations. First, weight and length data were obtained from health booklets and were not collected for research purposes, so variability in measurement precision is likely. Growth charts plotted for each participant were examined visually by 2 pediatricians, and a total of 209 (7%) measurements of weight or length were removed (eg, physiologically implausible measurements). Second, other than breastfeeding duration, we did not have nutritional data for the infancy period (eg, age at introduction of solid foods); confounding by early nutrition on associations of interest could not be investigated. Third, prepregnancy maternal weight status or weight gain during pregnancy were not available. In sensitivity analyses, however, estimated coefficients did not change following adjustment for maternal body mass index measured when participants were aged 8 to 10 years.

In sum, our findings suggest that it is not birth weight or postnatal weight gain during the first 2 years of life per se that predict cardiovascular risk factors in children; rather, gaining weight more rapidly up to 2 years of age sets the stage for the development of increased adiposity in childhood that then adversely affects lipid and BP levels in early adolescence. Efforts to promote healthy patterns of weight gain are likely needed throughout the life course, including prenatally, postnatally, and throughout childhood. These efforts may contribute to the prevention of childhood obesity and, ultimately, its deleterious consequences for cardiovascular health.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of QUALITY study participants included and of those excluded from the analytic sample

A total of 564 participants (out of 630 seen at baseline) completed a follow up visit at the age of 10-12 years. Of these, 395 met eligibility criteria for the current analysis: born at term (i.e., 37 to <42 completed weeks of gestation) and with complete anthropometric data at birth and up to 24 months of age (i.e., weight and length measured at birth, at least once between ages 1-12 months, and at least once between 12.1-24 months).

Characteristics	Included in analysis (n=395)	Excluded from analysis (n=169)	p value*
Sex, girls % (n)	43.0 (170)	47.9 (81)	0.28
% total body fat mass, mean (SD)	25.9 (10.7)	26.7 (11.0)	0.40
BMI category† at age 8-10 years, % (n)			
Normal weight	59.8 (236)	56.8 (96)	0.50
Overweight	18.2 (72)	22.5 (38)	
Obese	22.0 (87)	20.7 (35)	
Duration breastfed % (n)			
Never breastfed	19.2 (76)	21.4 (36)	0.84
Breastfed < 3 months	26.3 (104)	25.0 (42)	
Breastfed 3-6 months	24.1 (95)	21.4 (36)	
Breastfed > 6 months	30.4 (120)	32.1 (54)	
Child's age at follow up, years, mean (SD)	11.6 (0.9)	11.7 (0.9)	0.71
Lipids			
Total cholesterol, mmol/L, mean (SD)	3.7 (0.7)	3.8 (0.7)	0.31
LDL cholesterol, mmol/L, mean (SD)	2.2 (0.6)	2.3 (0.6)	0.16
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.2)	1.2 (0.3)	0.35
Triglycerides, mmol/L, mean (SD)	**0.8 (0.4)**	**0.7 (0.4)**	**0.049**
Blood pressure			
Systolic, mmHg, mean (SD)	97.7 (8.9)	96.7 (8.5)	0.24
Diastolic, mmHg, mean (SD)	**50.7 (5.3)**	**49.6 (5.2)**	**0.021**
Parental education, % (n)			
2 parents with high school degree or less	6.6 (26)	8.4 (14)	0.75
1 or 2 parents with technical degree	37.5 (148)	36.5 (61)	
1 or 2 parents with university degree	56.0 (221)	55.1 (92)	
Maternal age at conception of child, years, mean (SD)	30.1 (4.6)	29.5 (4.8)	0.19
Maternal BMI, kg/m^2, mean (SD)	29.2 (6.5)	29.9 (6.4)	0.20
In-utero exposure to gestational diabetes, % (n)	17.2 (68)	18.3 (31)	0.75
In-utero exposure to maternal hypertension, % (n)	9.87 (39)	13.2 (22)	0.25
In-utero exposure to maternal smoking, % (n)	**12.4 (49)**	**21.0 (35)**	**0.0097**

Abbreviations: BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; SD, standard deviation.

†BMI categories are based on World Health Organization cut-offs for sex and age adjusted BMI z-scores.

*p values for chi-square tests when comparing categorical variables and for t-tests when comparing continuous variables

Table S2. Comparison of participants at age 8-10 years and at age 10-12 years in a sub-sample (n=395) of the QUALITY Cohort

	8-10 years (Time 1)	10-12 years (Time 2)	Correlation of Time 1 to Time 2
Child's age at assessment, years, mean (SD)	9.6 (0.9)	11.6 (0.9)	0.98
Tanner stage, %			
Pre-pubertal (Tanner stage 1)	78.7	33.2	-
Pubertal (Tanner stages 2, 3, 4 or 5)	21.3	66.8	-
% total body fat mass, mean (SD)	25.9 (10.7)	28.4 (10.8)	0.91
Lipids			
Total cholesterol, mmol/L, mean (SD)	3.9 (0.7)	3.7 (0.7)	0.71
LDL cholesterol, mmol/L, mean (SD)	2.3 (0.6)	2.2 (0.6)	0.72
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.2)	1.2 (0.2)	0.66
Triglycerides, mmol/L, mean (SD)	0.81 (0.4)	0.8 (0.4)	0.66
Blood pressure			
Systolic, mmHg, mean (SD)	93.6 (8.2)	97.7 (8.9)	0.51
Diastolic, mmHg, mean (SD)	48.3 (5.1)	50.7 (5.3)	0.46

Table S3. Associations* of birth weight-for-length, postnatal weight gain and childhood adiposity with triglycerides and HDL cholesterol measured at age 10-12 years, stratified by sex, among 395 children of the QUALITY Cohort, Quebec, Canada, 2005-2011.

	Triglycerides		HDL cholesterol	
	Boys	**Girls**	**Boys**	**Girls**
Model 1: Adjusted for covariates				
Birth weight-for-length z-score	-3.7 (-10.1, 2.6)	2.2 (-4.5, 9.0)	0.2 (-2.4, 2.8)	-1.0 (-4.1, 2.1)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	1.5 (-0.5, 3.5)	0.1 (-2.5, 2.7)	-0.9 (-1.7, -0.02)	0.1 (-1.1, 1.3)
Model 2: Adjusted for covariates and % body fat				
Birth weight-for-length z-score	-5.2 (-11.2, 0.8)	-1.2 (-7.8, 5.4)	0.8 (-1.7, 3.3)	0.5 (-2.5, 3.5)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	0.7 (-1.2, 2.6)	-1.8 (-4.4, 0.9)	-0.6 (-1.3, 0.2)	0.9 (-0.3, 2.1)
% of total body fat (at 8-10 yrs)	1.7 (1.1, 2.3)	1.7 (0.9, 2.4)	-0.6 (-0.9, -0.4)	-0.7 (-1.1, -0.4)

Abbreviations: CI, confidence interval; HDL, high density lipoprotein.

*Statistically significant interactions were found for triglycerides between birth zWFL and sex (p=0.04) and between postnatal weight gain and sex (p=0.02), and for HDL-cholesterol between postnatal weight gain and sex (p=0.01).
Birth weight-for-length and postnatal growth in weight-for-length are entered simultaneously in Model 1 and models are adjusted child's age, parental education, gestational age, breastfeeding, and in-utero exposure to gestational diabetes, maternal hypertension and maternal smoking. Model 2 is as Model 1 but is further adjusted for % of body fat mass. β coefficients (95% CI) represent the % increase/decrease in the outcome for a 1-unit increase in the corresponding independent variable.

Table S4. Beta coefficients* for total, direct and indirect effects (mediated by % body fat at 8-10 years) of birth weight-for-length and of postnatal weight gain on triglycerides and on HDL cholesterol at 10-12 years, stratified by sex among 395 children of the QUALITY Cohort, Quebec, Canada, 2005-2011.

Effect	Triglycerides		HDL cholesterol	
	Boys	Girls	Boys	Girls
	B (SE), p-value			
Birth weight-for-length				
Total	-6.54 (2.55), 0.010	2.10 (2.91), 0.469	1.80 (1.06), 0.089	-1.11 (1.32), 0.400
Direct	-5.21 (2.96), 0.079	-1.19 (3.26), 0.714	0.77 (1.24), 0.536	0.50 (1.49), 0.736
Indirect	-1.34 (2.01), 0.506	3.3 (1.98), 0.095	1.04 (0.83), 0.212	-1.62 (0.89), 0.071
Postnatal weight gain				
Total	1.49 (0.99), 0.132	0.11 (1.28), 0.935	-0.85 (0.41), 0.038	0.10 (0.58), 0.858
Direct	0.72 (0.94), 0.441	-1.77 (1.29), 0.170	-0.56 (0.39), 0.156	0.91 (0.59), 0.121
Indirect	0.77 (0.38), 0.043	1.87 (0.59), 0.002	-0.30 (0.15), 0.045	-0.81 (0.26), 0.002

*Path analysis is applied for each outcome variable and for boys and girls separately. Models include the 2 main exposure variables (birth weight-for-length and postnatal weight gain), the suspected mediator (% body fat at 8-10 yrs) and covariates (child's age, parental education, gestational age, breastfeeding, and in-utero exposure to gestational diabetes, maternal hypertension and maternal smoking). β coefficients (95% CI) represent the % increase/decrease in the outcome for a 1-unit increase in the corresponding independent variable.

Table S5. Associations* of birth weight-for-length, postnatal weight gain and childhood adiposity with plasma lipids measured at age 10-12 years among QUALITY Cohort children born with an appropriate size for their gestational age (AGA), n=318

	Total cholesterol	LDL cholesterol	Triglycerides	HDL cholesterol
Model 1: Adjusted for covariates				
Birth weight-for-length z-score	-0.6 (-2.5, 1.3)	-0.6 (-3.4, 2.2)	-0.6 (-5.8, 4.6)	-0.7 (-3.0, 1.5)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	-0.2 (-0.9, 0.5)	-0.3 (-1.2, 0.7)	1.1 (-0.7, 3.0)	-0.4 (-1.2, 0.4)
Model 2: Adjusted for covariates and % body fat				
Birth weight-for-length z-score	-0.9 (-2.8, 1.0)	-1.1 (-3.9, 1.6)	-2.6 (-7.5, 2.4)	0.04 (-2.1, 2.2)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	-0.3 (-1.0, 0.4)	-0.5 (-1.5, 0.4)	0.2 (-1.6, 1.9)	0.03 (-0.7, 0.8)
% of total body fat (at 8-10 yrs)	0.2 (0.02, 0.4)	0.4 (0.2, 0.7)	1.6 (1.1, 2.1)	-0.7 (-0.9, -0.4)

Abbreviations: CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.

*Birth weight-for-length and postnatal growth in weight-for-length are entered simultaneously in Model 1 and models are adjusted child's age, sex, parental education, gestational age, breastfeeding, and in-utero exposure to gestational diabetes, maternal hypertension and maternal smoking. Model 2 is as Model 1 but is further adjusted for % of body fat mass. β coefficients (95% CI) represent the % increase/decrease in the outcome for a 1-unit increase in the corresponding independent variable.

Table S6. Associations* of birth weight-for-length, postnatal weight gain and childhood adiposity with blood pressure measured at age 10-12 years among QUALITY Cohort children born with an appropriate size for their gestational age (AGA), n=318

	Systolic BP z-score	Diastolic BP z-score
Model 1: Adjusted for covariates		
Birth weight-for-length z-score	0.03 (-0.06, 0.1)	-0.04 (-0.09, 0.01)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	0.03 (-0.002, 0.06)	-0.01 (-0.03, 0.008)
Model 2: Adjusted for covariates and % body fat		
Birth weight-for-length z-score	0.003 (-0.08, 0.9)	-0.05 (-0.1, -0.002)
Postnatal weight gain (0.5 weight-for-length z-score from 0-2 years)	0.02 (-0.01, 0.05)	-0.02 (-0.03, 0.002)
% of total body fat (at 8-10 yrs)	0.02 (0.01, 0.03)	0.009 (0.004, 0.01)

Abbreviations: BP, blood pressure; CI, confidence interval.

*Birth weight-for-length and postnatal growth in weight-for-length are entered simultaneously in Model 1 and models are adjusted for child's age, sex, parental education, gestational age, breastfeeding, and in-utero exposure to gestational diabetes, maternal hypertension and maternal smoking. Model 2 is as Model 1 but is further adjusted for % of body fat mass. β coefficients (95% CI) for BP z-scores based on values from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.

Table S7. Coefficients* for total, direct and indirect effects (mediated by % body fat at 8-10 years) of birth weight-for-length and of postnatal weight gain on cardiovascular risk at 10-12 years among QUALITY Cohort children born with an appropriate size for their gestational age (AGA), n=318

Effect	Total cholesterol	LDL cholesterol	Triglycerides	HDL cholesterol	Systolic BP z-score	Diastolic BP z-score
Birth weight-for-length						
Total	-0.3 (-1.9, 1.2)	-0.2 (-2.4, 2.1)	-2.4 (-6.7, 1.8)	-0.2 (-2.0, 1.7)	0.02 (-0.05, 0.09)	-0.02 (-0.06, 0.02)
Direct	-0.9 (-2.8, 1.0)	-1.1 (-3.8, 1.6)	-2.6 (-7.4, 2.3)	0.04 (-2.1, 2.2)	0.003 (-0.08, 0.08)	-0.05 (-0.1, -0.003)
Indirect	0.6 (-0.5, 1.7)	1.0 (-0.6, 2.6)	0.1 (-3.0, 3.2)	-0.2 (-1.6, 1.2)	-0.02 (-0.07, 0.03)	0.03 (-0.002, 0.06)
Postnatal weight gain						
Total	-0.2 (-0.8, 0.5)	-0.3 (-1.2, 0.7)	1.1 (-0.6, 2.9)	-0.4 (-1.2, 0.4)	0.03 (-0.001, 0.06)	-0.01 (-0.03, 0.007)
Direct	-0.3 (-1.0, 0.3)	-0.5 (-1.5, 0.4)	0.2 (-1.5, 1.9)	0.03 (-0.7, 0.8)	0.02 (-0.01, 0.05)	-0.02 (-0.03, 0.001)
Indirect	0.1 (-0.007, 0.3)	0.3 (0.03, 0.5)	1.0 (0.3, 1.7)	-0.4 (-0.7, -0.1)	0.01 (0.003, 0.02)	0.006 (0.0009, 0.01)

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.

*Path analysis was applied separately for each outcome variable, models include the 2 main exposure variables (birth weight-for-length and postnatal weight gain), the suspected mediator (% body fat at 8-10 yrs) and covariates (child's age, sex, parental education, gestational age, breastfeeding, and in-utero exposure to gestational diabetes, maternal hypertension and maternal smoking). β coefficients (95% CI) associated with lipid outcomes represent the % increase/decrease in the outcome for a 1-unit increase in the corresponding independent variable. β coefficients (95% CI) associated with BP outcomes represent an increase/decrease in BP z-score for a 1-unit increase in the corresponding independent variable.