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Association of Weight Gain in Infancy and Early Childhood with Metabolic Risk in Young Adults

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Context: Early postnatal life has been suggested as an important window during which risks for long-term health may be influenced.

Objective: The aim of this study was to examine the independent associations between weight gain during infancy (0–6 months) and early childhood (3–6 yr) with components of the metabolic syndrome in young adults.

Design: This was a prospective cohort study (The Stockholm Weight Development Study).

Setting: The study was conducted in a general community.

Participants: Subjects included 128 (54 males) singletons, followed from birth to 17 yr.

Main Outcome Measure: None of these young adults met the full criteria for the metabolic syndrome. We therefore calculated a continuous clustered metabolic risk score by averaging the standardized values of the following components: waist circumference, blood pressure, fasting triglycerides, high-density lipoprotein cholesterol, glucose, and insulin level.

Results: Clustered metabolic risk at age 17 yr was predicted by weight gain during infancy (standardized $\beta = 0.16$; $P < 0.0001$) but not during early childhood (standardized $\beta = 0.10$; $P = 0.23$), adjusted for birth weight, gestational age, current height, maternal fat mass, and socioeconomic status at age 17 yr. Further adjustment for current fat mass and weight gain during childhood did not alter the significant association between infancy weight gain with the metabolic risk score (standardized $\beta = 0.20$; $P = 0.007$).

Conclusions: Rapid weight gain during infancy (0–6 months) but not during early childhood (3–6 yr) predicted clustered metabolic risk at age 17 yr. Early interventions to moderate rapid weight gain even at very young ages may help to reduce adult cardiovascular disease risks. **(*J Clin Endocrinol Metab* 92: 98–103, 2007)**

BOTH INTRAUTERINE AND early postnatal life have been suggested as important windows during which risks for long-term health may be influenced (1). Low birth weight and thinner size at birth, which are markers of fetal growth restriction, have been linked to cardiovascular disease and metabolic syndrome risk (insulin resistance, impaired glucose tolerance, hypertension, dyslipidemia, and central fat) in adults (2–6). Postnatal rapid weight gain has also been associated with increased risk for obesity (7, 8), hypertension (9), insulin resistance (10), and increased mortality from cardiovascular disease later in life (11). These two early growth patterns are closely linked, because intrauterine growth-restricted infants usually compensate by showing a rapid ("catch-up") growth during the first year of life. It is suggested that it is this postnatal adaptation in growth, rather than low birth weight itself, that contributes more to later disease risks (7, 12). However, it is not clear whether the critical period of rapid weight gain in relation to development of long-term cardiovascular and metabolic risks occurs during the first months of life, in early childhood, or in both.

In a Swedish birth cohort study, we recently observed independent long-term effects of both infancy (0–6 months) and early childhood (3–6 yr) weight gain on fat mass at age 17 yr (13). We have now explored the relationships between infancy and early childhood weight gain on more detailed assessment of individual and clustered metabolic risk factors.

Subjects and Methods

Study design and population

SWEDES is a longitudinal study of weight development in offspring of mothers participating in the Stockholm Weight and Pregnancy Development Study (14, 15). Briefly, 1423 mothers were invited and followed up during and after their pregnancies in 1984–1985. The sample represented a mixed metropolitan population from both the inner city area of Stockholm and suburb districts with a distribution in social groups that corresponded reasonably well to the population in the Stockholm area. Four percent of the mothers were of non-Swedish origin, compared with 7.5% of the total population in 1984.

A total of 481 mothers and their children participated in the follow-up study (SWEDES) after 17 yr. In a subgroup of singletons (n = 128), complete data including height and weight development during infancy and childhood and body composition and fasting blood samples at follow-up were available and constitutes the sample for the present study. A detailed drop-out analysis between those mothers who were initially invited but were not participating in the present study (n =

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Abbreviations: BMI, Body mass index; CI, confidence interval; GLM, General Linear Modeling; HDL, high-density lipoprotein.

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1295) and participants (n = 128) did not reveal any significant differences in number of previous pregnancies; age, weight, height, and body mass index (BMI) before pregnancy; total weight gain during pregnancy; and BMI at 6 and at 12 months after pregnancy (all $P > 0.05$). At follow-up, 21.6% of the mothers were overweight (BMI > 25) and 8% were obese (BMI > 30), which is comparable to Swedish national data (16). Almost 80% of the mothers were categorized as white-collar workers.

Length of gestation, birth weight, and ponderal index in the offspring did not differ significantly between this subsample and the entire cohort. Furthermore, birth weight did not differ from Swedish growth reference (17) and varied between 2110 g and 4450 g (median, 3500 g). However, the mean BMI at age 17 yr was slightly lower in males compared with Swedish reference data (18) (20.1 *vs.* 20.9; $P = 0.02$), whereas no difference was observed in females (21.2 *vs.* 20.8, $P = 0.25$).

The local Ethical Committee of Huddinge University Hospital approved the study, and informed consent was obtained from each mother and each child.

Childhood follow-up

Birth weight and length were noted from hospital records. Ponderal index was calculated as birth weight/length^3 (kg·m^{-3}). Infancy length and weight were measured by standard clinical procedures during routine visits at the child welfare center at ages 6 months 1 yr and 2 yr, and thereafter height and weight were measured annually until age 6 yr. Gestation was estimated from the date of the last menstrual period reported by the mothers. A total of 124 births were at full-term (>36 wk gestation) and four children were born preterm (wk 33–36). Analysis of the data excluding these preterm children did not alter the results.

Maternal birth weight, smoking during pregnancy, and breast-feeding patterns were recorded on questionnaires during and after pregnancy. Similarly, maternal education, occupation, and monthly income during pregnancy and at follow-up were recorded by questionnaire. Mothers' occupation at follow-up was used as an indicator of socioeconomic status and coded on a scale from 1 to 6 (according to Statistics Sweden) (19). Smoking status (smoker *vs.* nonsmoker) in mothers and children was also recorded on a questionnaire at follow-up. All data collected in mothers were used as potential confounding factors when analyzing associations between the main exposures and outcomes.

Assessment at age 17 yr

Standing height was measured to the nearest 0.5 cm against a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg using the BodPod scale (Life Measurement Instruments, Concord, CA). BMI was determined as weight/height^2 (kg/m^{-2}). Waist circumference was measured to the nearest 0.5 cm in duplicate, at the minimum circumference between the iliac crest and the rib cage, with subjects standing dressed in underwear. Body volume was measured by air-displacement plethysmography using the BodPod, after adjustments for predicted thoracic lung volume and estimated surface area artifact (20). Fat mass, percentage body fat, and fat-free mass were calculated by the software provided by the manufacturer according to the equation by Siri (21). Body volume was measured in duplicate or triplicate when the initial two measures differed by more than 150 ml. All subjects were measured wearing tight-fitting underwear, or a swimsuit, and a swim cap. The same procedures were adopted for the mothers and the study participants, and each mother-offspring pair was measured in the fasting state on the same day at follow-up. A trained research nurse measured arterial blood pressure after 5 min of rest in the seated position with a standard manual sphygmomanometer. Venous blood was drawn into vacuum tubes, coagulated, and centrifuged at room temperature and immediately frozen at −20 C and stored at −70 C before analysis. Sexual maturity was assessed using the five-stage scale for breast development in females and pubic hair in males, according to Tanner (22). A dichotomous variable, puberty passed (Tanner stage V) *vs.* not passed (Tanner stage < V) was created. One hundred percent of the girls and 78% of the boys were postpubertal according to these criteria for pubertal development.

Assays

Lipoproteins were isolated from fresh serum by a combination of preparative ultracentrifugation and precipitation with a sodium phosphotungstate and magnesium chloride solution. Serum lipoproteins and triglycerides were assayed by enzymatic techniques using a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA). Plasma glucose was determined using the glucose oxidase method on an automatic glucose analyser. Plasma insulin was measured by an ELISA kit (Mercodia AB, Uppsala, Sweden) in a Bio-Rad Coda automated EIA analyzer (Bio-Rad Laboratories, Hercules, CA).

Informed consent was obtained from each mother and offspring and the local Ethical Committee of Huddinge University Hospital approved the study.

Calculations

Broadly based on the components suggested to constitute the metabolic syndrome (23), we constructed a standardized, continuously distributed metabolic risk score (z-score), which has been previously described in detail (24–26). Briefly, this score was derived by taking the average value of the standardized measures (z-scores) for the following six outcomes: waist circumference; (systolic blood pressure + diastolic blood pressure)/2; fasting plasma glucose; fasting plasma insulin; inverted fasting high-density lipoprotein (HDL) cholesterol; and fasting triglyceride levels. Because of their skewed distribution, fasting insulin and triglycerides were log transformed before calculating the z-score.

z-Scores were also internally derived for weight at birth, 6 months, 3 yr, and 6 yr to adjust for sex and age. Weight gain was calculated as the change in z-scores for weight between birth and six months ("infancy") and between 3 and 6 yr ("early childhood"). We validated this approach by also calculating external z-scores scores for weight by comparison with the Swedish growth reference (17), and all findings were essentially unchanged (data not shown).

Statistical procedures

Differences between genders were tested by ANOVA. Relationships between variables were assessed by correlation and partial correlation coefficients. The independent associations between infancy weight gain with individual components of the metabolic risk and the clustered metabolic risk score at age 17 yr were tested by General Linear Modeling (GLM, analysis of covariance), adjusting for gender, birth weight, gestational age, current height, maternal fat mass, and socioeconomic status (treated as a categorical variable). Similarly, the independent associations between childhood weight gain with individual and clustered metabolic risk was tested by GLM adjusting for the same confounders as noted. We thereafter introduced infancy weight gain and childhood weight gain in the same model and finally tested the interaction between these variables. Further adjustments were thereafter made for fat mass at age 17 yr to test whether the current level of adiposity would influence on the associations between infancy and childhood weight gain and later metabolic outcomes. In preliminary analyses we also adjusted for smoking status (smoker *vs.* nonsmoker) and sexual maturity (puberty passed *vs.* not passed). However, because these variables neither influenced the direction of the association nor contributed to the explained variation in any of the outcomes, they were excluded from the final models. Statistics were analyzed with SPSS for Windows (version 11.0) and a P value < 0.05 denoted statistical significance. Values reported are means ± SD unless otherwise stated.

Results

Physical and metabolic characteristics of the subjects are displayed in Table 1. At age 17 yr, 7.8% of participants were categorized as overweight (BMI > 25) and 2% were obese (BMI > 30). Three individuals had impaired fasting glucose (*i.e.* >5.6 mmol·liter^{-1}), eight individuals had HDL cholesterol levels less than 1.0 mmol·liter^{-1}, 10 had fasting triglycerides more than 1.7 mmol·liter^{-1}, and one individual had elevated systolic blood pressure (*i.e.* >140 mm Hg).

Infancy and early childhood weight gain

Gain in weight z-score between 0 and 6 months was inversely related to birth weight (partial r = −0.44, $P < 0.0001$,

TABLE 1. Characteristics of the subjects (n = 128)

	Males (n = 54)	Females (n = 74)
Age (y)	16.8 ± 0.4	16.7 ± 0.4
Weight (kg)	64.9 ± 10.3	58.6 ± 9.1[a]
Height (cm)	179.5 ± 6.3	166.3 ± 5.8[c]
BMI (kg·m^{-2})	20.1 ± 2.5	21.2 ± 2.7
Fat mass (kg)	9.8 ± 5.3	17.9 ± 6.3[a]
Fat free mass (kg)	55.1 ± 7.2	40.8 ± 4.3[a]
Waist circumference (cm)	72.9 ± 7.7	70.8 ± 6.6[c]
Glucose (mmol·liter^{-1})	4.84 ± 0.31	4.67 ± 0.38[b]
Insulin (mU·liter^{-1})[d]	7.88 (7.26–8.54)	6.68 (6.15–7.26)
HDL (mmol·liter^{-1})	1.27 ± 0.25	1.44 ± 0.34[b]
Triglycerides (mmol·liter^{-1})	0.87 ± 0.39	0.93 ± 0.50
Systolic blood pressure (mm Hg)	113.4 ± 9.4	108.4 ± 12.8[b]
Diastolic blood pressure (mm Hg)	63.9 ± 8.7	66.4 ± 9.5
Birth weight (g)	3539 ± 504	3375 ± 495[c]
Ponderal index (kg·m^{-3})	20.8 ± 2.37	20.4 ± 2.46

Data are mean (SD).
[a] $P < 0.0001$; [b] $P < 0.01$; [c] $P < 0.05$ for gender differences (*t* test).
[d] Geometric means and 95% CI.

adjusted for sex and gestational age). Gain in weight z-score between 3 and 6 yr was weakly inversely related to birth weight (partial r = −0.15, $P = 0.08$, adjusted for sex and gestational age) and was inversely related to weight gain between 0 and 6 months (partial r = −0.31, $P < 0.0001$), indicating that those who showed accelerated weight gain in infancy tended to slow down in early childhood. More subjects showed clinically significant rapid weight gain (defined as a gain in weight z-score >0.67, which is sufficient to result in upward centile crossing on clinical growth charts) (7) during infancy (0–6 months: n = 32/128, 25%) than during early childhood (3–6 yr: n = 15/128, 12%; χ^2: $P < 0.001$). Only two children showed rapid weight gain during both periods.

Outcomes at age 17 yr

Partial correlations, adjusted for gender between BMI, waist circumference, and metabolic outcomes at age 17 yr is shown in Table 2. Infancy weight gain was significantly ($P < 0.0001$) associated with clustered metabolic risk after adjusting for birth weight, gestational age, gender, current height, maternal fat mass, and socioeconomic status (Table 3). In contrast, childhood rapid weight gain ($P = 0.20$) was not associated with clustered metabolic risk after adjusting for the same confounders as described above (Table 4).

The association between infancy weight gain and clustered metabolic risk was independent after further adjustment for early childhood weight gain [$\beta = 0.20$, 95% confidence interval (CI), 0.08; 0.31]. Additional adjustment for self-reported physical activity did not change the observed associations between infancy rapid weight gain and clustered metabolic risk ($\beta = 0.17$, 95% CI, 0.06; 0.28).

TABLE 2. Partial correlations (adjusted for gender) between BMI, waist circumference, and metabolic outcomes in 17-yr-old adolescents (n = 128)

Metabolic outcome	BMI	Waist
Glucose (mmol·liter^{-1})	0.04 (0.70)	0.03 (0.79)
Insulin (mU·liter^{-1})	0.21 (0.02)	0.22 (0.017)
HDL (mmol·liter^{-1})	−0.18 (0.049)	−0.22 (0.015)
Triglycerides (mmol·liter^{-1})	0.19 (0.034)	0.23 (0.012)
Systolic blood pressure (mm Hg)	0.20 (0.024)	0.10 (0.25)
Diastolic blood pressure (mm Hg)	0.17 (0.06)	0.04 (0.64)

P values are in *parentheses*.

TABLE 3. Regression coefficients (95% CI) from the generalized linear models examining the independent association between infancy (0–6 months) rapid weight gain with clustered metabolic risk at age 17 yr (n = 128)

Predictor variables	β	95% CI	*P* value
Infancy weight gain (z-score)	0.16	0.05; 0.27	0.006
Birth weight (z-score)	0.10	−0.04; 0.25	0.14
Gestational age (wk)	0.005	−0.07; 0.08	0.89
Gender	0.21	−0.06; 0.49	0.13
Current height (cm)	0.02	−0.0001; 0.033	0.06
Maternal FM (kg)	−0.007	−0.02; 0.003	0.18
Maternal SES	−0.09	−0.19; 0.003	0.06

FM, Fat mass; SES, socioeconomic status.

Figure 1 displays the association between infancy rapid weight gain with clustered metabolic risk stratified according to clinically significant rapid (>0.67 SD), no change and slow (<0.67 SD) weight gain. In stratified analyses, rapid weight gain in infancy was significantly associated with clustered metabolic risk independently of childhood rapid weight gain and other confounding factors (*P* for trend = 0.005).

Table 4 shows the association between infancy weight gain and the individual components of the clustered metabolic risk. Infancy weight gain also predicted waist circumference ($P = 0.004$), blood pressure ($P = 0.021$), fasting triglycerides ($P = 0.008$), and HDL cholesterol ($P = 0.047$), and was borderline associated with fasting insulin ($P = 0.08$) in this model.

No significant interactions (all $P > 0.4$) were observed between birth weight, infancy weight gain, and childhood weight gain on any of the metabolic outcomes at age 17 yr. We finally substituted birth weight with ponderal index at birth as a confounding variable and reanalyzed our data and the results were materially unchanged (data not shown).

Adjustment for fat mass

As previously reported in this cohort, weight gain during both infancy and early childhood was positively associated with fat mass at age 17 yr (standardized regression coefficient: infancy: 0.33 [0.17; 0.49]; early childhood: 0.47 [0.25; 0.70]).

To assess whether the associations with infancy weight

TABLE 4. Regression coefficients (95% CI) from the GLMs examining the independent association between childhood (3–6 yr) rapid weight gain with clustered metabolic risk at age 17 yr (n = 128)

Predictor variables	β	95% CI	*P* value
Childhood weight gain (z-score)	0.10	−0.07; 0.27	0.23
Birth weight (z-score)	0.01	−0.12; 0.15	0.84
Gestational age (wk)	0.01	−0.06; 0.09	0.72
Gender	0.09	−0.21; 0.40	0.55
Current height (cm)	0.01	−0.005; 0.03	0.55
Maternal FM (kg)	−0.007	−0.017; 0.04	0.22
Maternal SES	−0.09	−0.20; 0.02	0.09

FM, Fat mass; SES, socioeconomic status.

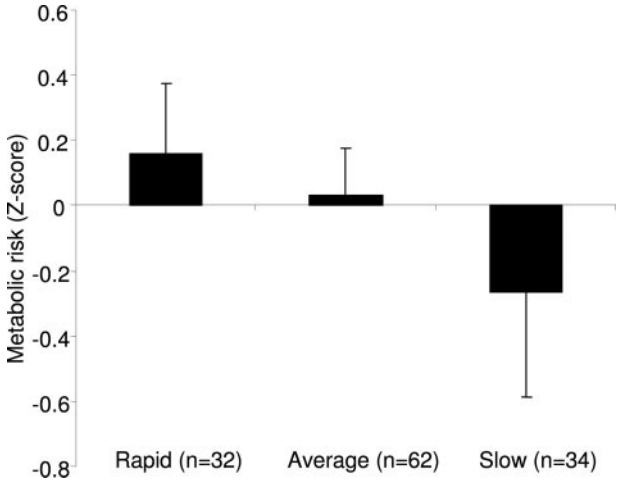

FIG. 1. Adjusted means (95% CI) of clustered metabolic risk score (z-score) by stratified groups of weight gain during infancy (0–6 months). Rapid (>0.67 weight SD gain), average, and slow (<0.67 weight SD gain) weight gain groups are equivalent to upward, no-change, and downward weight centile crossing, respectively, on standard growth charts. Data are adjusted for birth weight, rapid weight gain during childhood, gender, current height, mothers' fat mass, and socioeconomic status level (P for trend = 0.03).

gain were mediated by current adiposity, we reanalyzed the associations between infancy weight gain with the clustered metabolic risk score after excluding waist circumference from the score and by making further adjustment for current fat mass. Independent of current adiposity, the clustered metabolic risk score association with infancy weight gain remained significant (standardized $\beta = 0.17$; 95% CI: 0.05; 0.30; $P = 0.007$). Substituting current fat mass by BMI or waist circumference did not materially change the results.

Discussion

In this healthy contemporary prospective birth cohort we found that infancy rapid weight gain was associated with metabolic risk factors at age 17 yr. These observations were independent of birth weight, gestational age, rapid weight gain in childhood, current height, maternal fat mass, and socioeconomic status. Furthermore, no significant interactions were observed, indicating that the effects of infancy weight gain on later metabolic risk were the same irrespective of birth weight and subsequent weight gain in early childhood. Our findings are also consistent with data in murine models (27) and from infants born preterm (28–30) in suggesting that rapid weight gain during very early postnatal life may have adverse long-term implications for cardiovascular and metabolic health (31).

TABLE 5. Weight gain during infancy (0–6 months) related to the individual components of the metabolic syndrome z-score at age 17 yr in the SWEDES cohort (n = 128)

Outcome (SD)	Infancy weight gain (0–6 months)	95% CI	P value
Waist circumference	0.29	0.09; 0.49	0.004
Insulin	0.18	−0.03; 0.39	0.08
Glucose	0.06	−0.15; 0.27	0.57
Mean BP	0.22	0.03; 0.42	0.021
Triglycerides	0.30	0.08; 0.51	0.008
HDL cholesterol	0.21	0.003; 0.42	0.047

Outcomes are standardized regression coefficients (β) and 95% CI. Mean BP, Blood pressure (systolic blood pressure + diastolic blood pressure)/2; HDL, inverted HDL cholesterol. Weight gain and all outcomes were entered as z-scores in order to allow direct comparison of a 1-unit gain in infancy weight z-score on each outcome. Data are adjusted for gender, birth weight, childhood weight gain (3–6 yr), gestational age, current height, maternal fat mass, and socioeconomic status.

As in any observational study, we have to be cautious in inferring causality based on our findings. However, our findings were similar before and after adjusting for a number of potential confounding factors, such as birth weight and maternal BMI and socioeconomic status, and they were consistent in continuous and stratified analyses. Our results are also supported by previous observations that postnatal catch-up growth is associated with the metabolic syndrome in adult men (32, 33). However, those studies defined catch-up growth as the ratio of weight at age 18 yr to birth weight (32), or as the difference in weight SD scores between birth and age 49–51 yr (33), and our current study provides much more precise information on the timing of the rapid postnatal weight gain that appears to be detrimental to later health. Other more contemporary studies with more detailed data on childhood growth are consistent with our findings, but those studies have much shorter duration of follow-up and less detailed assessment of metabolic disease risks (34, 35).

We expressed metabolic syndrome risk as a continuous standardized combined score broadly based on the World Health Organization-defined outcome variables (23). Preliminary data suggest that this score has greater statistical power than the conventional categorical outcomes (36). However, none of our young adults reached the full criteria for the metabolic syndrome (23), and it will be important to confirm our findings with longer-term outcomes such as cardiovascular disease. All of the metabolic syndrome components, except for fasting glucose, showed similar positive trends for association with infancy weight gain. Because these components are closely interrelated, we had insufficient power to confidently assess which of the individual metabolic components may be likely to be most directly effected by rapid weight gain. However, we were able to distinguish apparently independent effects of rapid infancy weight gain on body fat mass and other metabolic outcomes.

We have previously reported that rapid weight gain during infancy predicted greater fat mass at age 17 yr (13). Much of the contributions of rapid infancy weight gain to later metabolic syndrome risks may therefore be mediated through larger body fat mass in young adult life. However, after removing the adiposity component (*i.e.* waist circumference) from the metabolic syndrome risk score and adjusting for current fat mass (or waist circumference), rapid weight gain during the first 6 months of life remained significantly associated with clustered metabolic risk. This could possibly indicate an early programing of adult metabolic risk through other morphological, metabolic, or hormonal mechanisms (37).

Our study sample, based on availability of early growth measurements and full metabolic outcome data at age 17, did not differ regarding birth weight from the larger cohort, or

indeed from Swedish reference data (17). The limited number of low birth weight (*i.e.* <2500 g) individuals (n = 6) in our cohort formally reduced our ability to test whether the observed associations were similar across birth weight groups. However, low-birth-weight infants usually compensate their growth restriction by rapid infant weight gain, and the predicted effect on later metabolic outcomes of this catch-up growth could be even more pronounced. At follow-up, our young adult males were slightly leaner compared with Swedish reference data (18), and the prevalence of overweight and obesity was lower compared with national data (16). It is unlikely that this would confound the observed associations, but it may have attenuated the strength of the associations.

In our previous report based on a larger sample of this cohort, rapid weight gain during early childhood (between 3 and 6 yr) predicted greater fat mass at age 17. However, in the current study early childhood weight gain was not significantly associated with clustered metabolic risk at 17; a weak positive was seen and it is possible that this would have reached significance in a larger sample. Furthermore, it is possible that in other populations in which excess weight gain during early childhood is more common, or in which rates of childhood and adult obesity are higher, then early childhood weight gain could explain a greater proportion of later metabolic disease risks (38, 39). We are, however, cautious to generalize our findings to other populations, and they need to be confirmed in larger prospective birth cohorts from different socioeconomic and cultural settings.

In conclusion, rapid weight gain during infancy is associated with long-term adverse effects on body composition and metabolic risk factors independent of birth weight, rapid childhood weight gain, and other putative confounding factors. Early interventions to moderate rapid weight gain even at very young ages could potentially help to reduce adult cardiovascular disease risks.

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