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Infant Body Composition and Adipokine Concentrations in Relation to Maternal Gestational Weight Gain

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OBJECTIVE

To investigate associations of maternal gestational weight gain and body composition and their impact on offspring body composition and adipocytokine, glucose, and insulin concentrations at age 4 months.

RESEARCH DESIGN AND METHODS

This was a prospective study including 31 mother-infant pairs ($N = 62$). Maternal body composition was assessed using doubly labeled water. Infant body composition was assessed at 4 months using air displacement plethysmography, and venous blood was assayed for glucose, insulin, adiponectin, interleukin-6 (IL-6), and leptin concentrations.

RESULTS

Rate of gestational weight gain in midpregnancy was significantly associated with infant fat mass ($r = 0.41$, $P = 0.03$); rate of gestational weight in late pregnancy was significantly associated with infant fat-free mass ($r = 0.37$, $P = 0.04$). Infant birth weight was also strongly correlated with infant fat-free mass at 4 months ($r = 0.63$, $P = 0.0002$). Maternal BMI and maternal fat mass were strongly inversely associated with infant IL-6 concentrations ($r = -0.60$, $P = 0.002$ and $r = -0.52$, $P = 0.01$, respectively). Infant fat-free mass was inversely related to infant adiponectin concentrations ($r = -0.48$, $P = 0.008$) and positively correlated with infant blood glucose adjusted for insulin concentrations ($r = 0.42$, $P = 0.04$). No significant associations for leptin were observed.

CONCLUSIONS

Timing of maternal weight gain differentially impacts body composition of the 4-month-old infant, which in turn appears to affect the infant's glucose and adipokine concentrations.

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Intrauterine exposure to diabetes (1,2), obesity (3), and excessive maternal gestational weight gain (4,5) are hypothesized to affect fetal growth and development, which is reflected in babies being born small or large for gestational age to women who were obese and/or diabetic during pregnancy. Previous studies have shown that maternal glucose is positively associated with infant adiposity at

birth and in later childhood, and offspring of obese and type 2 diabetic mothers are also at higher risk of obesity (6) and type 2 diabetes (7) during adulthood.

The mechanisms through which intrauterine exposures affect the metabolic outcomes of the offspring are poorly understood; however, undernutrition (8), overnutrition (9,10), hormone imbalance, and accelerated growth (11,12) of the fetus are thought to be pivotal factors in these processes. In utero, the glucose-stimulated hormone insulin is particularly relevant, owing to its anabolic properties, whereas in the postpartum period, adipocyte-derived hormones involved in insulin signaling and adipogenesis (13,14), such as interleukin-6 (IL-6) (15), adiponectin (16) and leptin (17), may be mechanistically relevant for infant growth and metabolism.

In diabetic pregnancies, the fetal pancreas is often exposed to excessive glucose and protein levels, which stimulate growth primarily through the overproduction of insulin by the fetal pancreas, sometimes resulting in macrosomia (18). The heavier birth weight of babies born to some diabetic pregnancies is reflective of this process, where the stressed pancreas accelerates growth via the anabolic actions of insulin (18); this process is also hypothesized to diminish the capacity of the pancreatic β-cells to function adequately across the adult life span, thus raising the trajectory for diabetes even before the baby is born.

Although the mechanisms through which these processes occur are poorly understood, overweight and obesity in offspring of diabetic pregnancies are well documented (19,20), highlighting a potential mediating role of adipocyte-derived hormones in these relationships. Excess adiposity, particularly around the abdomen, causes insulin resistance, a major precursor to diabetes (21). Thus, excessive weight gain in pregnancy, when coupled with β-cell dysfunction, can cause gestational diabetes. Defining the mechanisms that link excessive gestational weight gain with early-life metabolic disturbances may help identify targets for early-life interventions aimed at reducing the risk of chronic cardiometabolic disease in the offspring later in life.

The purpose of this study was to determine the relationship between maternal weight gain and infant body composition and plasma glucose and insulin concentrations at 4 months of age. We also sought to establish the role of candidate adipokines (IL-6, leptin, and adiponectin) in mediating these relationships, as these hormones have established roles in adult obesity and diabetes (17,22).

RESEARCH DESIGN AND METHODS

This study has been described in detail elsewhere (23,24). Participants were recruited through local media advertising and contact with midwives at local antenatal clinics. A total of 35 pregnant women from Västerbotten County, a region in the north of Sweden, were enrolled in the study. Three women withdrew from the study before delivery; the remaining 32 women successfully delivered. One woman gave birth to dizygotic twins, resulting in a total of 18 female and 15 male newborns. The twin pregnancy was excluded from these analyses. Gestational data were collected from the women at between 28 and 32 weeks of gestation during study visits at the Clinical Research Center at Umeå University Hospital. All but one of the women participated in the follow-up study visit, which occurred between 11 and 19 weeks postpartum. Written informed consent was provided by the mothers for all aspects of the study protocol. Written assent was provided by the mothers for participation of their infants. Additional pregnancy data were collected with permission from participant medical records. This study was approved by the Regional Ethical Review Board in Umeå, Sweden.

Assessment of Maternal Body Composition and Gestational Weight Gain

Height (to the nearest 0.5 cm) and weight (to the nearest 0.1 kg) were measured at between 28 and 32 gestational weeks using a calibrated wall-mounted stadiometer and a calibrated digital scale (Tanita Corporation, Tokyo, Japan), respectively. Maternal height and weight were also abstracted from medical records at weeks 8–16 and 36–41. BMI was calculated by dividing weight (kg) by height squared (m^2) (kg/m^2). Body composition (fat and fat-free mass) was estimated using the doubly labeled water method (25). Participants were given a body weight–dependent oral dose of stable isotopes (0.07 g ^2H_2O and 0.174 g $H_2^{18}O$ per kg body weight). A predose urine sample was collected prior to the administration of the oral dose, and 10 subsequent urine samples were collected, one for each of the 10 days after the day of dosing. Total body water was calculated as the average of the linearly regressed isotope dilution spaces at time 0, correcting by 1.01 and 1.04, respectively, to account for the exchange of isotopes with nonaqueous components within the body. Fat-free mass was then calculated by dividing body mass by the hydration factor of 0.747, with the difference between body weight and lean tissue equating to the fat mass (26).

Infant Body Composition and Biochemistry at 4 Months of Age

Infants were assessed at a mean (SD) age of 4.25 (2.0) months.

Body length and weight were measured using a measuring board (CMS Weighting Equipment Ltd., London, U.K.) and a calibrated digital scale (Seca; ErgoNordic AB, Bromma, Sweden), respectively. Body length was measured to the nearest 0.1 cm, and weight was measured to the nearest 1 g. Air displacement plethysmography (PeaPod; Life Measurement Inc., Concord, CA) was used to estimate (without clothing or diaper) fat mass and fat-free mass standardized by computing a z score by age and sex (mean 0, SD 1). Gestational age- and sex-matched averages from the Swedish population were used to standardize early infancy weight of the infants (27).

A venous blood sample was drawn from the back of the infant's hand after a minimum 2 h without feeding. Anesthetic cream was applied to the hand at the area of the blood draw 1 h prior to collection. Samples were obtained in EDTA and serum tubes,

immediately placed on ice, processed, and sent to the hospital Clinical Biochemistry Laboratory for analysis or stored at −80°C pending subsequent analyses. Serum IL-6 concentrations were determined using a high-sensitivity ELISA kit (R&D Systems, Abingdon, U.K.). Intra- and interassay coefficients of variation were 7.5 and 8.9%, respectively. Plasma leptin was measured by an "in house" radioimmunoassay, validated against the commercially available Linco assay, as previously described (28). Plasma adiponectin concentrations were determined using an ELISA kit (R&D Systems). The intra- and interassay coefficients of variability were <7.5%. Serum glucose and insulin levels were measured at the Clinical Biochemistry Laboratory at Umeå University Hospital. Serum glucose concentrations were analyzed using VITROS 5, 1 FS Chemistry System (Ortho-Clinical Diagnostics, Raritan, NJ), and serum insulin concentrations were measured through a microparticle enzyme immunoassay (Abbott Imx; Abbott Laboratories, Abbott Park, IL).

Statistical Analysis

All infant continuous biologic and anthropometric variables were standardized by age and sex (z scores). Rate of gestational weight gain in midpregnancy was calculated as the difference in weight from the 8–16-week prenatal visit prior to the study and the 28–32-week study visit divided by the number of weeks between weight measurements. Rate of gestational weight gain in late pregnancy was calculated in a similar way using the 28–32- and 36–41-week visits and dividing by the number of weeks between measurements. All rates of gestational weight gain are expressed as kilograms per week. Relationships between maternal characteristics and infant body composition, growth, and biochemical markers were evaluated using Spearman correlations adjusted for maternal age, gestational age at measurement, and parity. Correlation analyses, including measurements of midpregnancy rate of gestational weight gain, were additionally adjusted for gestational age at the first weight measurement; correlations including

measurements of late-pregnancy rate of gestational weight gain were additionally adjusted for gestational age at the last weight measurement. Differences between infant measures by sex were evaluated using Wilcoxon–Mann-Whitney nonparametric tests. All analyses were performed using SAS software (V9.2; SAS Institute, Cary, NC).

RESULTS

Characteristics of the mothers and infants are shown in Table 1.

Associations between rates of maternal weight gain during different periods in pregnancy and infant body composition are shown in Fig. 1.

Maternal Body Composition, Infant Body Composition, and Glucose and Insulin Concentrations

Infant birth weight was positively correlated with late pregnancy weight gain (r = 0.40, P value = 0.02). Infant birth weight was strongly correlated with infant fat-free mass at 4 months of age (r = 0.63, P value = 0.0002). Infant fat-free mass was positively correlated

with infant glucose adjusted for insulin (r = 0.42, P value = 0.04).

Potential Mediating Role of Adipokines

As shown in Table 2, maternal adiposity (BMI and fat mass) was strongly inversely correlated with infant IL-6 concentrations. Infant fat-free mass was inversely related to infant adiponectin concentrations. No statistically significant associations were evident for leptin concentrations. Leptin, IL-6, adiponectin, glucose adjusted for insulin, and insulin were weakly correlated with mid- and late pregnancy, although not statistically significant (refer to Supplementary Table 1).

CONCLUSIONS

Maternal obesity and elevated glucose concentrations during pregnancy increase the risk of type 2 diabetes in the offspring (19,29). Little is known about the biological mechanisms underlying these relationships, although obesity in the offspring is thought to be an important mediating factor (7,19,30).

Table 1—Maternal and infant characteristics

Mothers (n = 31)			
Age (years)	30.8 (3.6)		
Early-pregnancy BMI (kg/m^2)[1]	23.0 (4.9)		
Midpregnancy BMI (kg/m^2)[2]	25.5 (3.6)		
Late-pregnancy BMI (kg/m^2)[3]	27.7 (4.2)		
Midpregnancy weight gain (kg/week)	0.39 (0.22)		
Late-pregnancy weight gain (kg/week)	0.55 (0.46)		
Second and third trimester weight gain			
(kg/week)	0.46 (0.23)		
Midpregnancy fat mass (kg)	22.8 (9.3)		
Midpregnancy fat-free mass (kg)	50.0 (7.0)		
Infants (n = 31)	Boys (n = 16)	Girls (n = 15)	P value
Gestational age at delivery (weeks)	40.3 (1.1)	40.6 (2.0)	0.91
Birth weight (g)	3,575 (357)	3,470 (875)	0.32
Birth weight z score	−0.43 (0.79)	−0.61 (1.45)	0.81
Age at assessment (weeks)	17.0 (2.0)	17.0 (2.0)	0.7
Weight (g)	**6,975 (690)**	**6,235 (1,075)**	**0.02**
Length (cm)	**64.2 (2.3)**	**61.5 (2.9)**	**0.01**
Fat mass (g)	1,890 (550)	1,613 (952)	0.19
Fat-free mass (g)	**5,071 (288)**	**4,524 (953)**	**0.02**
IL-6 (pg/mL)	0.65 (1.75)	0.54 (0.24)	0.56
Adiponectin (μg/mL)	39.1 (7.5)	38.8 (7.5)	0.93
Leptin (ng/mL)	4.0 (1.6)	4.9 (2.9)	0.17
Fasting glucose (mmol/L)	4.4 (0.5)	4.4 (0.4)	0.81
Fasting insulin (mIU/L)	3.6 (2.1)	3.3 (3.5)	0.91

Data are medians (SDs). All maternal variables were measured at 28–32 weeks unless otherwise specified. All infant variables were measured at 11–19 weeks postpartum unless otherwise indicated. P value is for Wilcoxon–Mann-Whitney test comparisons between sexes. Results in bold text are statistically significant (P value < 0.05). [1]At 10–16 weeks' gestation. [2]At 28–32 weeks' gestation. [3]At 36–38 weeks' gestation. IU, international units.
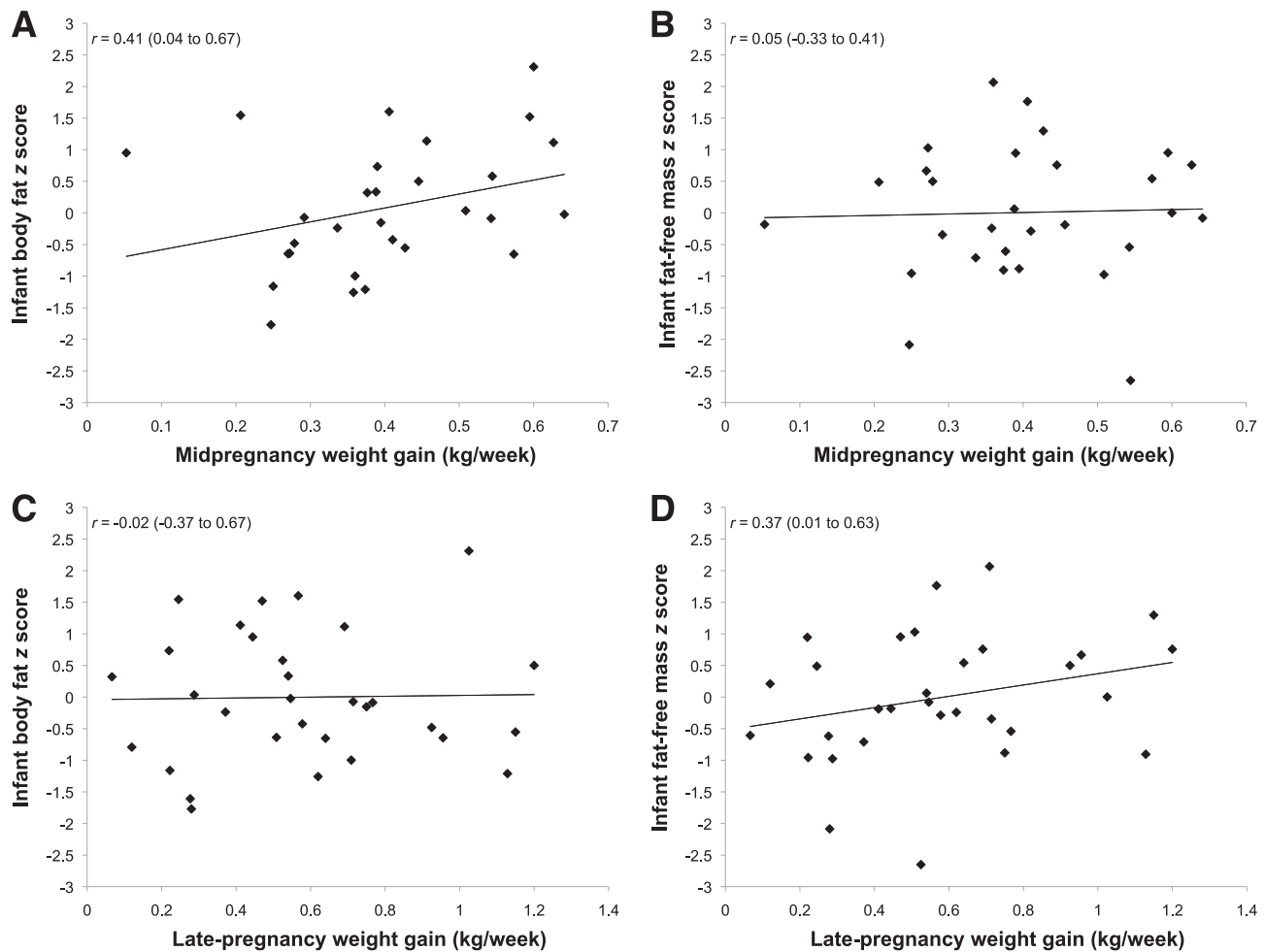
Figure 1—Infant body composition by maternal gestational weight gain. Statistics are Spearman partial correlation coefficients and 95% CIs. *A*: Correlation between midpregnancy rate of maternal weight gain and infant body fat mass *z* score. *B*: Correlation between midpregnancy rate of maternal weight gain and infant fat-free mass *z* score. *C*: Correlation between late-pregnancy rate of maternal weight gain and infant body fat mass *z* score. *D*: Correlation between late-pregnancy rate of maternal weight gain and infant fat-free mass *z* score.

Here we aimed to elucidate the early life factors that are relevant to these processes by comparing maternal body composition and rate of weight gain during pregnancy with infant body composition and glucose and insulin concentrations. Additionally, we sought to investigate the mediating role of adipokines as a secondary aim of this study.

We have previously studied the relationship between maternal body composition during pregnancy and infant body composition at 4 months postpartum (24). To extend those observations, we examined whether infant adipokine (IL-6, leptin, or adiponectin) concentrations impact this relationship and showed that maternal adiposity (BMI and fat mass) was

strongly inversely related to infant IL-6 concentrations at 4 months. Infant fat-free mass was also inversely related to infant adiponectin concentrations (an insulin signaling cytokine [31]) and positively related to glucose adjusted for insulin (Table 2), suggesting that leaner infants may be less insulin sensitive. No significant associations were noted for leptin. Although previous studies report a positive relationship between leptin concentration and maternal adiposity (17), in our study, no significant associations were noted for leptin at 4 months. Although one possibility is that these associations disappear in early infancy, it could also be that our study is underpowered to test these associations.

A novel finding in our study is that the rate of gestational weight gain at different periods in pregnancy is differentially associated with infant body composition at 4 months of age. The rate of weight gain in midpregnancy was strongly associated with infant fat mass, whereas the rate of weight gain during late pregnancy was strongly associated with infant fat-free mass. The former observation is supported by a study on prenatal fat development in 805 human embryos and fetuses, indicating that the gestational age between 14 and 29 weeks constitutes the critical window determining adipogenesis (32). The study provides histological evidence that adipose tissue differentiation occurs in early gestation between the 14th and 16th weeks of

Table 2—Correlations between maternal and infant anthropometry and infant metabolic biomarkers

	Infant biochemical markers at 4 months of age				
	IL-6 (n = 23)	Leptin (n = 23)	Adiponectin (n = 23)	Glucose adjusted for insulin (n = 24)	Insulin (n = 25)
Maternal variables					
BMI (kg/m^2)	**−0.60 (−0.81 to −0.23)**	−0.12 (−0.50 to 0.31)	0.06 (−0.36 to 0.46)	0.29 (−0.13 to 0.61)	0.05 (−0.35 to 0.44)
Fat mass (kg)	**−0.52 (−0.76 to −0.13)**	−0.11 (−0.50 to 0.31)	0.04 (−0.38 to 0.44)	0.20 (−0.22 to 0.56)	0.10 (−0.31 to 0.47)
Fat-free mass (kg)	−0.11 (−0.49 to 0.32)	−0.41 (−0.70 to 0.01)	−0.25 (−0.60 to 0.18)	0.23 (−0.19 to 0.58)	0.09 (−0.32 to 0.47)
Infant variables					
Birth weight (kg)	−0.05 (−0.45 to 0.37)	−0.29 (−0.63 to 0.14)	−0.12 (−0.50 to 0.31)	0.10 (−0.32 to 0.49)	0.02 (−0.38 to 0.42)
Fat mass (kg) at 4 months	−0.26 (−0.60 to 0.18)	0.22 (−0.22 to 0.57)	−0.08 (−0.47 to 0.35)	0.23 (−0.19 to 0.58)	−0.16 (−0.52 to 0.28)
Fat-free mass (kg) at 4 months	−0.19 (−0.55 to 0.25)	−0.10 (−0.49 to 0.33)	**−0.48 (−0.74 to −0.07)**	**0.42 (0.01 to 0.70)**	0.09 (−0.13 to 0.61)
Glucose adjusted for insulin (mmol/L) at 4 months	**−0.65 (−0.84 to −0.31)**	−0.04 (−0.45 to 0.39)	−0.12 (−0.52 to 0.32)		
Insulin (mIU/L) at 4 months	0.02 (−0.40 to 0.44)	−0.01 (−0.43 to 0.42)	−0.22 (−0.58 to 0.23)	0.09 (−0.13 to 0.61)	

Statistics are Spearman partial correlation coefficients (95% CIs). All infant variables are age- and sex-standardized z scores. Infant glucose was additionally adjusted for infant insulin levels except in the correlation between infant glucose and insulin. All maternal variables were measured at 28–32 weeks' gestation and were adjusted for gestational week, age, and parity. All infant variables were measured at 11–19 weeks. Results in bold text are nominally statistically significant at P value < 0.05.

gestation and is then followed by fat-cell proliferation until the 23rd week of gestation, and any growth thereafter may be attributed to an increase in the size, and not in the number, of existing fat lobules (32). Thus, it may be that early pregnancy, notably when fat formation occurs, is particularly susceptible to levels of signaling hormones present in the intrauterine milieu.

A previous study that examined the rate of gestational weight gain and offspring body composition found that women who gained excessive amounts of weight (33) during pregnancy had offspring with greater adiposity at birth compared with the offspring of women who gained an appropriate amount of gestational weight (5). However, that study did not look at weight gain by trimester and only measured adiposity at birth and not at other time points during infancy.

A study by Davenport et al. (34) reported that weight gain in the first half of pregnancy is related to greater adiposity in the infant at birth. Our findings add to this by showing that higher adiposity resulting from early pregnancy weight is still evident at 4 months. Another study by Fraser et al. (30) examined gestational weight gain (per 400 g/week) during trimesters and later adiposity in the offspring at 9 years of age. In their study of 5,154 mother-offspring pairs, there was a positive association between gestational weight gain in early pregnancy (0–14 weeks) and offspring adiposity, and this association strengthened in mothers who had an average weight gain >500 g/week. In mid- and late pregnancy (14–36 weeks), however, the association between maternal weight gain and offspring adiposity was found only in mothers who gained >500 g/week. There were also positive and linear associations between maternal weight gain in mid- and late pregnancy and adverse lipid and inflammatory profiles in the offspring at 9 years of age, which were reportedly mediated by offspring adiposity.

The relationship of maternal characteristics and infant adipokines and inflammatory markers has

previously been studied in fetal cord blood (35,36), but not to our knowledge in early infancy. In a study among 121 predominantly Caucasian women, cord blood IL-6 concentrations were significantly higher in obese mothers compared with lean mothers (35). By contrast, in a study among 20 Mexican women, maternal adiposity was associated with lower cord blood IL-6 concentrations (36). In our study, we found strong negative correlations between maternal midpregnancy BMI and adiposity and infant IL-6 measured at approximately 4 months of age. In adults, elevated IL-6 levels (around four- to fivefold higher than seen in the present study) have been associated with greater diabetes risk (37). Yet, IL-6 has pleiotropic roles and in muscle can lower glucose levels by promoting fatty acid oxidation and basal- and insulin-stimulated glucose uptake (38). Although IL-6 is known to induce insulin resistance by activating SOC-3, a suppressor of cytokine signaling proteins that has been shown to inhibit insulin signaling, IL-6 simultaneously recruits GLUT4 to the plasma membrane in muscle cells, thereby enhancing glucose uptake via a noninsulin-mediated pathway (39). Moreover, the impact of IL-6 on glucose regulation depends on the concentration and duration of exposure to IL-6, as well as the presence of other molecules such as insulin and IL-10, where chronic exposure to low-dose IL-6 may result in adverse effects on insulin action (39,40). It may be that in our study of healthy infants, the net effect of IL-6, at levels well below those seen in diseased adults, is opposite to its deleterious effect on glucose control previously observed in obese adults, such that IL-6 at 4 months of age is associated with lower birth weight, lower glucose adjusted for insulin, and higher levels of insulin.

We also found that infant adiponectin was negatively correlated with infant fat-free mass. Previous studies have reported negative associations between early infancy growth (16) and infant length (31) and adiponectin. In our study, infant length and infant fat-free mass were strongly positively correlated (data not shown). It is possible that a

mechanism similar to the one underlying the associations between infant length, growth, and adiponectin is behind the associations between infant fat-free mass and adiponectin observed here.

Although state-of-the-art techniques were used here to phenotype the study participants, our study is limited by its relatively small sample size, which makes it difficult to determine if a nonsignificant finding is truly negative. Nevertheless, our study was adequately powered to test the primary hypotheses, in part because we used methods that are both precise and accurate. Although a number of findings are nominally statistically significant and we tested a priori hypotheses that were informed by existing evidence, some of these findings will be sensitive to type 1 error owing to the multiple tests performed, which should be considered when interpreting the study's results. Breast-feeding is well known to influence infant growth. At the time of the infant assessment, only 10% of the women were exclusively formula feeding their infants and 55% were exclusively breast-feeding. There were no significant correlations between infant feeding practice and growth, body composition, or adipokine levels, likely due to the small proportion of women who did not breast-feed their infants in this cohort. Although it is likely that even in exclusively breast-fed infants, variation in the amount of milk consumed during feeding influences growth to some extent, we did not collect such detailed information in the current study. A further limitation of our study is that it is not possible using observational data such as ours to determine cause and effect, and the trials that have been published do not address the topics we have examined. Additionally, although our data suggest that certain adipokines mediate the relationship of gestational weight gain and infant body composition, our study was underpowered to conduct formal mediation analyses.

Our findings suggest that timing of gestational weight gain impacts the development of muscle and adipose tissue in infant offspring. We also observed associations between

maternal body composition and infant glucose and IL-6 concentrations, and between infant fat-free mass and adiponectin levels, which may mediate the relationship of maternal gestational weight gain and infant body composition.

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