Associations of maternal BMI and gestational weight gain with neonatal adiposity in the Healthy Start study[1–5]

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ABSTRACT

Background: Maternal obesity and weight gain during pregnancy are risk factors for child obesity. Associations may be attributable to causal effects of the intrauterine environment or genetic and postnatal environmental factors.

Objective: We estimated associations of maternal prepregnancy body mass index (BMI) and gestational weight gain (GWG) overall and in early pregnancy, midpregnancy, and late pregnancy with neonatal adiposity.

Design: Participants were 826 women enrolled in a Colorado prebirth cohort who delivered term infants (2010–2013). GWG to 39 wk of gestation was predicted by using mixed models, and early pregnancy, midpregnancy, and late pregnancy rates of GWG (0–17, 17–27, and 27 wk to delivery) were calculated from repeated weight measures. Neonatal body composition was measured by using air-displacement plethysmography ≤3 d after birth.

Results: Each1-kg/m^2 increase in maternal BMI was associated with increased neonatal fat mass (5.2 g; 95% CI: 3.5, 6.9 g), fat-free mass (7.7 g; 95% CI: 4.5, 10.9 g), and percentage of body fat (0.12%; 95% CI: 0.08%, 0.16%). Each 0.1-kg/wk increase in predicted GWG was associated with increased fat mass (24.0 g; 95% CI: 17.4, 30.5 g), fat-free mass (34.0 g; 95% CI: 21.4, 46.6 g), and percentage of body fat (0.55%; 95% CI: 0.37%, 0.72%). No interaction was detected between BMI and GWG in their effects on neonatal body composition. Early pregnancy, midpregnancy, and late pregnancy rates of GWG were independently associated with fat mass and percentage of body fat. Midpregnancy and late pregnancy GWGs were associated with fat-free mass. An observed GWG that exceeded recommendations was associated with higher neonatal fat mass and fat-free mass but not percentage of body fat relative to adequate GWG.

Conclusions: Maternal prepregnancy BMI and GWG, including period-specific GWG, were positively and independently associated with neonatal adiposity. Associations of early and midpregnancy weight gain with neonatal adiposity support the hypothesis that greater maternal weight gain during pregnancy, regardless of prepregnancy BMI, is directly related to offspring adiposity at birth. The Healthy Start study was registered as an observational study at clinicaltrials.gov as NCT02273297. *Am J Clin Nutr* 2015;101:302–9.

Keywords adiposity, developmental origins, gestational weight gain, obesity, pregnancy

INTRODUCTION

Pediatric obesity is a critical public health problem, with 18% of US elementary school-aged children classified as obese in 2009–2010 (1). Childhood obesity is associated with numerous cardiovascular and metabolic conditions including dyslipidemia, hypertension, and insulin resistance (2) and may lead to a reduced quality of life (3) and reduced life expectancy (4). Studies suggested that a child's trajectory toward becoming obese may be set by influences very early in life (5). In a study of children aged 5–14 y, who subsequently developed obesity, nearly one-half of them were already overweight at age 5 y, and more than one-third of them were large at birth (6). This early onset suggests an etiologic contribution from prenatal and early postnatal environments.

The intrauterine environment has been shown to influence offspring obesity risk in the context of maternal gestational diabetes and prepregnancy obesity (7, 8). Moreover, several studies showed excessive gestational weight gain (GWG) to be associated with increased risk of large-for-gestational-age birth (9, 10) as well as offspring overweight or adiposity in childhood (11, 12), adolescence (13), and adulthood (14). Childhood obesity likely reflects a combination of prenatal and postnatal influences. However, the adiposity of a neonate at birth cannot be influenced by postnatal exposures and, therefore, may provide a useful window into the effects of the intrauterine environment. Some studies have focused on neonatal body fat measured by using a variety of methods including skinfold thickness (15, 16), dual-energy X-ray absorptiometry (17), and air-displacement plethysmography (18). These

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[4] Supplemental Table 1 is available from the online "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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studies reported positive associations of GWG with neonatal adiposity, but results varied regarding the role of maternal prepregnancy BMI and timing of GWG.

It has been proposed that early and midpregnancy GWG, which primarily represent increased maternal fat rather than the weight of the growing fetus (19), may be causally linked to offspring adiposity through the increased availability of maternal fuels such as glucose, amino acids, and free fatty acids (12, 20). However, few studies have examined associations between neonatal body composition and GWG occurring in specific periods of pregnancy.

Our aim was to estimate associations of maternal prepregnancy BMI and overall GWG as well as period-specific rates of GWG with neonatal adiposity measures in a large, ethnically diverse population. We hypothesized that maternal prepregnancy BMI and GWG would be positively associated with neonatal fat mass and the percentage of body fat, and early pregnancy, midpregnancy, and late pregnancy rates of GWG would be positively and independently associated with neonatal adiposity.

SUBJECTS AND METHODS

Study participants

Participants were enrolled in the Healthy Start study, which is an ongoing prospective cohort study that recruited ethnically diverse pregnant women from prenatal obstetrics clinics at the University of Colorado Hospital in 2010–2014. Women were excluded if they were expecting multiple births; had a previous stillbirth or preterm birth <25 wk of gestation; had pre-existing diabetes, asthma managed with steroids, cancer, or psychiatric illness; were younger than 16 y of age; or had already completed 24 wk of gestation. Participants provided written informed consent. The study was approved by the Colorado Multiple Institutional Review Board. The Healthy Start study was registered as an observational study at clinicaltrials.gov as NCT02273297.

Additional eligibility criteria for this analysis included the delivery of a live-born term infant (≥37 wk of gestation) between 19 March 2010 and 31 October 2013 with whole-body air-displacement plethysmography measurements within 3 d of birth and complete information on the following covariates: maternal age, race, education, household income, prepregnancy BMI, smoking during pregnancy, gravidity, predicted GWG to 39 wk (defined in Assessment of maternal BMI and GWG), infant gestational age at delivery, and infant sex. For period-specific analyses, eligible participants further had at least one measured weight in each of the following intervals: 14–20 and 24–30 wk of gestation.

Data collection

Participants were invited to the following 3 in-person research visits: the first visit was during early pregnancy (median: 17 wk), the second visit was during midpregnancy (median: 27 wk), and the third visit was after the delivery of their infant. Questionnaires administered by study personnel collected information on demographic characteristics, personal and family medical histories, and behaviors during pregnancy. Participants consented to allow study-related information to be abstracted from their medical records.

Measurement of neonatal body composition

Neonatal body composition was measured by using whole-body air-displacement plethysmography with the PEA POD device (COSMED) designed for infants between birth and 6 mo of age (21). The PEA POD device uses a 2-compartment model to measure fat mass (i.e., adipose tissue) and fat-free mass (i.e., bone, water, and nonbone mineral and protein). Whole-body air-displacement plethysmography was shown to produce highly reproducible measurements of the percentage of body fat in infants that did not differ significantly from those produced by the reference 4-compartment model (22). The PEA POD device was administered by trained clinical personnel at least twice for each infant; if the percentage of body fat differed >2%, the test was repeated a third time. For each outcome, the average of the 2 closest measures was used. The neonatal percentage of body fat was calculated as fat mass in grams divided by the sum of fat mass and fat-free mass in grams.

Assessment of maternal BMI and GWG

Maternal height was measured by research personnel by using a stadiometer at the first study visit. Weights were measured by research staff at each study visit and medical personnel at prenatal care visits during pregnancy. Weight before pregnancy was recorded by a medical provider at the first prenatal visit (91%) or self-reported at the first research visit (9%). Previous studies have noted high levels of agreement between maternal self-reported prepregnancy weight and prepregnancy weights obtained from medical records or research study data (23, 24). Maternal prepregnancy BMI was calculated as prepregnancy weight divided by height squared. When BMI (in kg/m^2) categories were used, we used the following classification system: underweight, <18.5; normal weight, 18.5–24.9; overweight, 25.0–29.9; and obese, ≥30.0 (25).

Weight gain was calculated by using 3 different approaches. The first approach defined observed GWG as the difference between the last available weight measurement during pregnancy and the prepregnancy weight. The mean (±SD) gestational age at the last available weight measurement was 38.2 ± 3.2 wk. A total of 94% of participants had last available weight measures recorded at or after 34 completed weeks of gestation. Observed GWG measures were classified as insufficient, adequate, or excessive according to the Institute of Medicine (IOM) 2009 guidelines (26).

The second approach used a mixed-effects model to predict GWG over a standardized length of gestation of 39 wk on the basis of all available pregnancy weight measurements as well as maternal age, race-ethnicity, height, and BMI before pregnancy. Participants with ≥4 measures of weight during pregnancy were included. The median number of weight measures per participant was 13 measures, and the maximum number was 23 measures. We evaluated all possible 2-, 3-, and 4-way interactions between predictors, including time, time squared, time cubed, and the covariates previously listed, by using a planned backward-selection approach to model fitting. A random effect of the individual was included to accommodate repeated measures of weight for each participant and allow individual-specific intercept and slope terms. The overall weekly rate of GWG was calculated by subtracting the model-predicted weight at 0 wk of gestation from the model-predicted weight at 39 wk of gestation and dividing the difference by 39 wk.

In the third approach, we calculated observed period-specific weekly rates of GWG in early pregnancy, midpregnancy, and late pregnancy. An early pregnancy rate was calculated by subtracting the prepregnancy weight from the weight measured nearest to 17 wk of gestation (within a 6-wk window) and dividing the difference by the number of weeks elapsed between weight measures. A midpregnancy rate was calculated in a similar manner by subtracting the 17-wk estimate from the weight measured nearest to 27 wk of gestation (within a 6-wk window) and dividing by the number of weeks elapsed. A late pregnancy rate was calculated by subtracting the 27-wk estimate from the last recorded pregnancy weight measurement and dividing by the number of weeks elapsed.

Covariates

Other variables were obtained from prenatal questionnaires or medical records. Maternal age at delivery was calculated by subtracting the participant's date of birth from the date of delivery. Household income in the previous year, maternal education, maternal smoking during pregnancy, number of previous pregnancies, and maternal race and ethnicity were self-reported via study questionnaires. Gestational age at birth was based on an estimated conception date created by averaging ≤4 recorded gestational-age estimates during pregnancy. These estimates were either reported by the participant at research visits or recorded by the provider on the prenatal medical record.

Statistical analysis

To evaluate associations of prepregnancy BMI and the continuous, predicted rate of GWG with neonatal adiposity measures, we fit separate multiple linear regression models for each neonatal outcome (fat mass, fat-free mass, and the percentage of body fat). We first estimated unadjusted associations between continuous maternal prepregnancy BMI and each continuous neonatal outcome as well as unadjusted associations between the continuous rate of overall model-predicted GWG and each continuous neonatal outcome. We fit a common adjusted model for each of the 3 neonatal adiposity outcomes, which included both BMI and the predicted rate of GWG as predictors as well as potential confounders. We assessed the possible effect-measure modification of main effects of BMI and GWG by the other variable in each adjusted model by including an interaction term between GWG and prepregnancy BMI and removing the term if the type III sum of squares was nonsignificant at $\alpha = 0.05$. We evaluated the assumption of linearity by plotting residuals of each model and examining graphs for deviations from normality.

Potential confounders were identified a priori on the basis of causal diagrams representing associations reported in the previous literature. Adjusted estimates for the main effects of prepregnancy BMI and predicted overall rate of GWG were obtained from a common, adjusted model that also included the following covariates: maternal age at delivery, gravidity, smoking during pregnancy, maternal education, race-ethnicity, household income, infant sex, postnatal age in days at body-composition measurements, and gestational age at birth. The following variables were treated as categorical variables with the following classifications used: gravidity (no previous pregnancies compared with any), smoking during pregnancy (none compared with any), maternal education (<12th grade, high school degree or General Educational Development, some college or associate's degree, 4 y of college, or a graduate degree), race-ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, or other), infant sex (male compared with female), household income (≤$40,000, $40,001 to $70,000, ≥$70,001, or do not know).

We estimated unadjusted and covariate-adjusted associations between the IOM category of observed overall and period-specific rates of GWG (insufficient, adequate, or excessive) and each continuous neonatal outcome by using linear regression models. Potential confounders included as covariates in the model were the same as previously stated with the exception that prepregnancy BMI was included as a categorical variable to match IOM classifications (<18.5, 18.5–24.9, 25.0–29.9, and ≥30). A possible effect-measure modification by prepregnancy BMI of the association between the category of GWG and neonatal adiposity was assessed in each adjusted model by including an interaction term between the IOM category of GWG and category of prepregnancy BMI and removing the term if the type III sum of squares was nonsignificant at $\alpha = 0.05$.

Finally, we estimated associations between the rate of GWG in early pregnancy, midpregnancy, and late pregnancy and each of neonatal adiposity outcomes. We first entered each of the 3 period-specific observed GWG rates in separate single-exposure linear regression models for each outcome adjusted for the covariates previously listed. We fit a common, adjusted model including rates of GWG in all 3 periods to identify independent effects of an increase in the rate of GWG in each period and holding constant the rate of gain in the other periods. We used an omnibus F test to assess whether period-specific associations differed significantly from one another at $\alpha = 0.04$. If the omnibus test was significant, pairwise associations were tested at $\alpha = 0.01$.

With recognition that the inclusion of a separate category for missing data could introduce bias (27), we performed a sensitivity analysis in which we treated participant responses of do not know for household income as missing. We then used multiple imputation (by using SAS PROC MI and PROC MIANALYZE; SAS Institute) to fill in missing values of income and repeated the analyses previously described. All statistical analyses were conducted with SAS 9.3 software (SAS Institute).

RESULTS

Of 1132 women enrolled in the Healthy Start study with a delivery date before 31 October 2013, 16 women experienced fetal demise, and 8 women terminated consent before delivery. Of the remaining women, 1000 individuals had a documented gestational age at birth ≥37 wk. Of these women, 827 individuals completed body-composition measurements ≤3 d of delivery. One participant was missing information on prepregnancy weight and was excluded, which left 826 participants in the main analysis. In period-specific analyses, a subset of 752 women with available weight measures in all 3 periods was used.

The 826 participants in the main analysis resembled the 1000 potentially eligible participants as well as the 752 participants in period-specific analyses with regard to maternal age, prepregnancy BMI, income, education, race-ethnicity, gravidity, smoking, mode of delivery, infant sex, and gestational age of the infant at birth (**Supplemental Table 1**). A slightly higher frequency of below-recommended GWG was observed in the 1000 potentially eligible participants (many of whom had no neonatal body-composition

measures taken at birth) compared with that of the 826 and 752 women eligible for analyses.

Of the 826 women in the main analysis, the mean age at delivery was 28 y, and the range was 16–43 y (**Table 1**). Approximately 20% of participants were obese before pregnancy (BMI ≥ 30); the mean prepregnancy BMI was 25.8. Participants were predominantly non-Hispanic white (53%), Hispanic (24%), or non-Hispanic black (17%), with 6% of women from other racial and ethnic groups. As expected, the observed GWG was highest in women who were underweight before pregnancy and lowest in women who were obese before pregnancy. However, women who were overweight or obese before pregnancy were more likely to exceed IOM recommendations for GWG than were women who were normal weight or underweight before pregnancy (data not shown).

When the observed GWG was classified by 2009 IOM recommendations (26), 21% of participants gained insufficient weight overall, 27% of participants gained adequate weight, and 51% of participants gained excessive weight (Table 1). When we examined period-specific rates of GWG relative to IOM recommendations, 51% of participants had an excessive gain in early pregnancy, 69% of participants had an excessive gain in midpregnancy, and 65% of participants had an excessive gain in late pregnancy; however, only 23% of subjects had excessive GWG in all 3 periods of pregnancy (data not shown). Observed and predicted overall GWG measures had similar means and medians (**Table 2**) and were highly correlated ($r = 0.92$, $P < 0.001$). The mean observed weekly rate of GWG increased from early pregnancy (0.17 kg/wk) to midpregnancy (0.55 kg/wk) and remained relatively constant into late pregnancy (0.54 kg/wk) (**Figure 1**).

Maternal BMI before pregnancy and the weekly rate of continuous predicted GWG were both positively associated with neonatal body size and body composition (**Table 3**). For each 1-kg/m^2 increase in maternal prepregnancy BMI, neonatal fat mass increased by 5.21 g (95% CI: 3.54, 6.89 g), fat-free mass increased by 7.71 g (95% CI: 4.50, 10.91 g), and the percentage of body fat increased by 0.12% (95% CI: 0.08%, 0.16%). For each 0.1-kg/wk increase in the overall rate of GWG, neonatal fat mass increased by 23.95 g (95% CI: 17.37, 30.53 g), fat-free mass increased by 33.95 g (95% CI: 21.35, 46.56 g), and the percentage fat mass increased by 0.55% (95% CI: 0.37%, 0.72%). There was no evidence of a statistical interaction between prepregnancy BMI and continuous predicted GWG in their associations with any outcomes.

The differences in magnitude between associations with prepregnancy BMI and GWG may be explained by the different SDs of BMI (SD: 6.3) and GWG (SD: 0.15 kg/wk) in our study population. The changes in neonatal body-composition measures associated with 1-SD unit increases in prepregnancy BMI and GWG were of similar magnitude (data not shown).

Adjustments for covariates strengthened some associations but did not materially change the results. With the removal of each covariate individually from the fully adjusted model, we determined that the adjustment for the rate of GWG was primarily responsible for the higher adjusted association of prepregnancy BMI with neonatal fat-free mass. We attributed this finding to the fact that prepregnancy BMI was inversely associated with GWG ($r = -0.27$, $P < 0.0001$), and the results of the unadjusted model were biased because of confounding by GWG.

Women with insufficient overall GWG according to IOM guidelines had offspring with lower fat mass and a lower percentage of body fat but no significant difference in offspring fat-free mass compared with for women with adequate GWG in adjusted models (**Table 4**). Women with excessive GWG had offspring with greater fat mass and also greater fat-free mass than did women with adequate GWG but no significant

TABLE 1
Characteristics of 826 participants who delivered term infants in 2010–2013

Characteristic	Values
Maternal age at delivery (y), *n* (%)	
16–19	106 (13)
20–24	161 (19)
25–29	205 (25)
30–34	248 (30)
35–43	106 (13)
Maternal BMI before pregnancy (kg/m^2), *n* (%)	
<18.5	26 (3)
18.5–24.9	428 (52)
25.0–29.9	205 (25)
≥30.0	167 (20)
Maternal race-ethnicity, *n* (%)	
Non-Hispanic white	440 (53)
Hispanic	198 (24)
Non-Hispanic black	137 (17)
Other	51 (6)
Maternal education completed, *n* (%)	
<12th grade	119 (14)
High school degree or General Educational Development	151 (18)
Some college or associate's degree	192 (23)
4 y of college (BA, BS)	191 (23)
Graduate degree (Master's, Ph.D.)	173 (21)
Annual household income in previous year, *n* (%)	
≤$20,000	127 (15)
$20,001–$40,000	117 (14)
$40,001–$70,000	144 (17)
≥$70,001	271 (33)
Do not know	167 (20)
Number of previous pregnancies, *n* (%)	
None	289 (35)
At least one	537 (65)
Maternal smoking during pregnancy, *n* (%)	
None	753 (91)
Any amount	73 (9)
Maternal observed gestational weight gain overall, *n* (%)	
Less than recommended	175 (21)
Within recommended range	227 (27)
More than recommended	424 (51)
Mode of delivery, *n* (%)	
Cesarean	175 (21)
Noncesarean	648 (79)
Infant gestational age at birth (wk), *n* (%)	
37–38	214 (26)
39–40	517 (63)
41–43	95 (12)
Sex of infant, *n* (%)	
M	426 (52)
F	400 (48)
Infant total body mass, g	3145 ± 411[1]
Infant fat mass, g	294 ± 150
Infant fat-free mass, g	2851 ± 325
Infant percentage of body fat	9.1 ± 3.9

[1]Mean ± SD (all such values).

TABLE 2
Distributions of observed and model-predicted GWG variables among 826 participants[1]

		Percentiles				
Variable	Mean ± SD	5th	25th	50th	75th	95th
Observed GWG to delivery, kg	14.3 ± 6.6	4.5	10.2	14.1	18.0	25.4
Model-predicted GWG to 39 wk, kg	14.6 ± 6.0	5.3	11.2	14.5	17.9	24.3
Model-predicted rate of GWG overall, kg/wk	0.37 ± 0.15	0.13	0.29	0.37	0.46	0.62

[1]GWG, gestational weight gain.

difference in the offspring percentage of body fat in adjusted models. Findings were similar when observed period-specific rates were compared with IOM guidelines for the rate of GWG in each trimester of pregnancy (data not shown). There was no evidence of effect modification by category of prepregnancy BMI of associations between the IOM category of GWG adequacy and any neonatal adiposity outcomes.

All 3 continuous period-specific observed rates of GWG were associated with neonatal fat mass, fat-free mass, and the percentage of body fat in models that contained only one period-specific rate as a predictor (**Table 5**). When models were further adjusted for rates of weight gain in the other 2 periods, associations between each of the period-specific rates of GWG and outcomes of neonatal fat mass and the percentage of body fat remained significant, whereas the association of early pregnancy GWG and fat-free mass became nonsignificant. There were no significant differences between early pregnancy, midpregnancy, and late pregnancy rates of GWG in the strength of their associations with fat mass ($P = 0.63$), fat-free mass ($P = 0.45$), or the percentage of body fat ($P = 0.64$) as assessed by using an omnibus test in the mutually adjusted model. We assessed the degree of variance inflation in the fully adjusted model and showed no evidence of multicollinearity.

In a sensitivity analysis, we treated responses of do not know for household income as missing data, and we performed a multiple imputation to fill in these missing covariate values. A reanalysis with the imputed data did not change the interpretation of any results (not shown).

DISCUSSION

In a large, multiethnic prebirth cohort study, we showed positive and independent associations of continuous maternal prepregnancy BMI and GWG with neonatal adiposity measures. Period-specific rates of GWG in early pregnancy, midpregnancy, and late pregnancy were independently associated with neonatal fat mass and the percentage of body fat, and midpregnancy and late pregnancy rates of GWG were associated with neonatal fat-free mass. Excessive overall GWG by IOM recommendations was associated with fat mass and fat-free mass but not adiposity (percentage of body fat) in adjusted models.

Our results are consistent with the findings of previous studies that reported that maternal prepregnancy BMI was positively associated with neonatal fat mass (28, 29) and add additional support to the hypothesis that maternal GWG is independently associated with neonatal adiposity at birth. Four previous studies specifically examined the association between GWG and offspring body composition at birth, which was assessed by using a variety of methods as follows: skinfold measurements (15, 16), dual-energy X-ray absorptiometry (17), and air-displacement plethysmography (18). All 4 studies classified GWG as excessive, adequate, or insufficient by IOM guidelines. Each of these studies had ~50% of participants with excessive GWG, which was similar to the proportion in our population. However, some of the previous studies excluded underweight women (15, 18), smokers (15), or women with abnormal glucose tolerance during pregnancy (16). Only one of the previous studies was conducted in an ethnically diverse population (18), and only one study

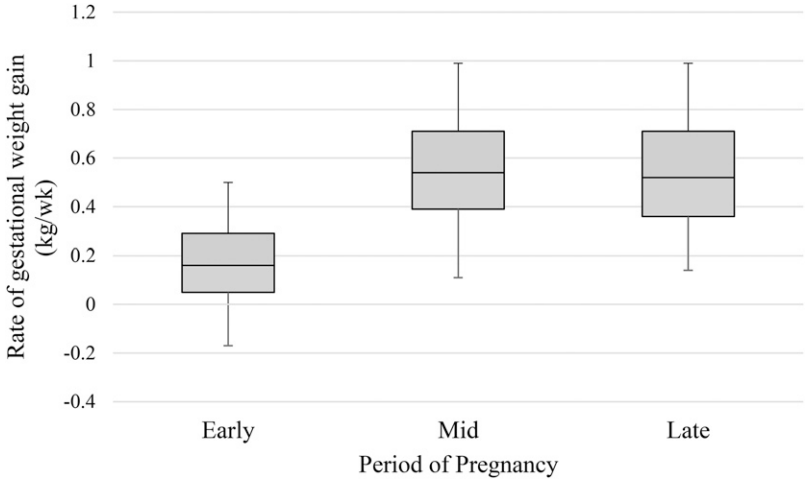

FIGURE 1 Observed rates (5th and 95th percentiles of the distribution) of gestational weight gain in early pregnancy (0–17 wk), midpregnancy (17–27 wk), and late pregnancy (27 wk to delivery) in 752 pregnancies. mid, midpregnancy.

TABLE 3
Associations of prepregnancy BMI and gestational weight gain with neonatal body composition in 826 participants[1]

	Prepregnancy BMI		Predicted rate of gestational weight gain to 39 wk	
	Unadjusted, increase per 1 kg/m^2 (95% CI)	Adjusted, increase per 1 kg/m^2 (95% CI)	Unadjusted, increase per 0.1 kg/wk (95% CI)	Adjusted, increase per 0.1 kg/wk (95% CI)
Fat mass, g	4.12 (2.53, 5.72)	5.21 (3.54, 6.89)	17.30 (10.68, 23.91)	23.95 (17.37, 30.53)
Fat-free mass, g	4.48 (0.99, 7.97)	7.71 (4.50, 10.91)	35.35 (21.01, 49.68)	33.95 (21.35, 46.56)
Percentage of body fat	0.10 (0.06, 0.14)	0.12 (0.08, 0.16)	0.37 (0.19, 0.54)	0.55 (0.37, 0.72)

[1]Common adjusted models included the following variables: prepregnancy BMI, predicted gestational weight gain to 39 wk, maternal age, race-ethnicity, education, household income, gravidity, gestational age at birth, infant sex, infant age at body-composition measurements, and maternal smoking during pregnancy. The increase in each neonatal outcome corresponding to a 1-kg/m^2 increase in prepregnancy BMI was estimated by using separate linear regression models. The increase in each neonatal outcome corresponding to a 0.1-kg/wk increase in the predicted rate of gestational weight gain was estimated by using separate linear regression models.

examined GWG in early or late pregnancy (15). Our sample was ethnically diverse and was larger than in any of the 4 previous studies, which had sample sizes between 172 and 564 (15–18). Contrary to the results of some previous studies (16, 18) but consistent with the findings of another study (17), we observed no evidence of a statistical interaction between prepregnancy BMI and GWG in their associations with neonatal adiposity.

The influence of maternal GWG on neonatal adiposity may differ according to the timing of weight gain during pregnancy. The only previous study that specifically addressed the timing of GWG showed that early excessive weight gain was associated with greater neonatal fat mass and the percentage of body fat than was late excessive weight gain (15). We examined the rate of GWG in 3 periods of pregnancy and observed positive associations between the rate of gain in each of the 3 periods and neonatal fat mass and the percentage of body fat, even after holding constant the rate of gain in other periods. We also showed independent associations between midpregnancy and late pregnancy rates of GWG and neonatal fat-free mass. We interpret the positive associations between early and midpregnancy GWG and neonatal adiposity as evidence of the influence of maternal fat accumulation and the intrauterine environment. The interpretation of the observed associations between late pregnancy GWG and fat mass or fat-free mass is complicated by the fact that fetal and placental weights constitute a larger fraction of weight gain in late pregnancy (19). However, we observed positive associations between the rate of GWG in all 3 periods and the neonatal percentage fat mass, which suggested that neonatal fat mass may increase more rapidly than fat-free mass in response to maternal GWG.

To make our results comparable with those of previous studies, we further examined the adequacy of observed weight gain according to IOM guidelines in association with neonatal body-composition measures. We showed positive associations between excessive GWG by IOM guidelines, relative to adequate GWG, and neonatal fat mass and fat-free mass. However, we did not observe a significant association between excessive GWG and the neonatal percentage of body fat. These results suggest that

TABLE 4
Adequacy of weight gain according to Institute of Medicine 2009 guidelines and neonatal body composition in 826 participants[1]

	Unadjusted		Adjusted	
Body-composition measure	Mean	β coefficient (95% CI)	Covariate-adjusted mean	β coefficient (95% CI)
Neonatal fat mass, g				
Less than recommended	—	−46.51 (−75.54, −17.47)	—	−42.25 (−70.50, −14.00)
Within recommended range	286.68	—	270.05	—
More than recommended	—	32.52 (8.78, 56.26)	—	24.31 (1.02, 47.60)
Neonatal fat-free mass, g				
Less than recommended	—	−95.66 (−158.27, −33.05)	—	−42.15 (−95.58, 11.28)
Within recommended range	2827.57	—	2788.02	—
More than recommended	—	84.56 (33.38, 135.75)	—	68.60 (24.57, 112.64)
Neonatal percentage of body fat				
Less than recommended	—	−1.10 (−1.86, −0.34)	—	−1.12 (−1.86, −0.38)
Within recommended range	8.97	—	8.57	—
More than recommended	—	0.64 (0.02, 1.26)	—	0.47 (−0.14, 1.08)

[1]Adjusted models were adjusted for maternal age, race-ethnicity, education, household income, prepregnancy BMI (<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2), gravidity, gestational age at birth, infant sex, infant age at body-composition measurements, and maternal smoking during pregnancy. β coefficient represents the change in each neonatal body composition outcome associated with the gestational weight gain adequacy category, relative to the within recommended range category and was estimated by using multiple linear regression models.

TABLE 5
Period-specific observed rates of GWG and neonatal body composition in 752 participants[1]

Continuous period-specific rate of GWG	Model 1, increase per 0.1 kg/wk (95% CI)	Model 2, increase per 0.1 kg/wk (95% CI)
Neonatal fat mass, g		
Early pregnancy	8.29 (3.89, 12.69)	8.12 (3.84, 12.41)
Midpregnancy	10.48 (6.75, 14.22)	9.07 (5.28, 12.85)
Late pregnancy	8.61 (4.85, 12.37)	6.19 (2.40, 9.98)
Neonatal fat-free mass, g		
Early pregnancy	8.47 (0.05, 16.89)	7.97 (−0.26, 16.20)
Midpregnancy	16.01 (8.86, 23.16)	12.48 (5.21, 19.75)
Late pregnancy	18.28 (11.15, 25.41)	15.05 (7.77, 22.33)
Neonatal percentage of body fat		
Early pregnancy	0.18 (0.07, 0.30)	0.18 (0.07, 0.29)
Midpregnancy	0.24 (0.14, 0.34)	0.21 (0.11, 0.31)
Late pregnancy	0.19 (0.09, 0.29)	0.13 (0.03, 0.23)

[1]Period-specific GWG variables were calculated in a subset of women with observed weight-gain measures at required intervals. Model 1 was adjusted for maternal age, race-ethnicity, education, household income, prepregnancy BMI, gravidity, gestational age at birth, infant sex, infant age at body-composition measurements, and smoking during pregnancy. Model 2 was adjusted as for model 1 and for the other 2 period-specific rates of GWG. The increase in each neonatal outcome corresponding to a 0.1-kg/wk increase in the observed rate of GWG was estimated by using multiple linear regression models. Early pregnancy was defined as ~0–17 wk, midpregnancy was defined as 17–27 wk, and late pregnancy was defined as 27 wk to delivery. GWG, gestational weight gain.

excessive GWG by IOM guidelines is more-strongly associated with total body mass than adiposity. Higher total body mass at birth has been associated with higher risk of subsequent child, adolescent, and adult obesity (30–33).

One strength of the analysis was the use of a predictive model to standardize the length of time over which overall GWG was calculated. Conventionally, GWG is calculated by subtracting prepregnancy weight from the last observed pregnancy weight. Because the estimate of the last observed pregnancy weight depends crucially on the length of the pregnancy, this approach may produce biased effect estimates in studies of outcomes that are also associated with gestational duration (34). With the use of a predictive model, we estimated GWG for a standard pregnancy length of 39 wk. Overall observed and predicted measures of GWG were highly correlated, which was likely related to the fact that we restricted our analysis to term pregnancies (34). With the use of an accurate predictive model and common time interval, we eliminated one source of bias in estimating associations between GWG and neonatal body composition, both of which may depend on the gestational age at birth. One limitation of our approach was that the 2-stage modeling procedure we used may have introduced some degree of measurement error in the exposure. We anticipated, on the basis of recent statistical literature (35), that this error would not have produced a bias in the estimate but may have inflated the variability of second-stage effect estimates.

There are plausible biological mechanisms by which maternal obesity and GWG may lead to increased neonatal adiposity. The fetal overnutrition hypothesis proposes that excess maternal circulating glucose crosses the placenta, resulting in increased fetal insulin secretion (36). Fetal hyperinsulinemia, in turn, may promote adipogenesis or adipose cell hypertrophy (37). Higher circulating free fatty acids and triglycerides associated with maternal obesity and excessive GWG may cause increased fatty acid transfer to the fetus, thereby promoting the development of larger or more-numerous fetal fat cells (20).

In addition to the mechanisms linking GWG to neonatal adiposity, other biological mechanisms were proposed by which fetal overnutrition may influence offspring's later risk of obesity. Long-term effects may be mediated through dysregulation of the hypothalamic-endocrine system that regulates appetite and satiety (38, 39) and the epigenetic alteration of genes related to leptin signaling (40). It is possible that all of these physiologic mechanisms operate together to increase offspring's risk of obesity in addition to or perhaps synergistically with a genetic predisposition.

The 2009 IOM report on weight gain during pregnancy emphasized the need for an investigation into the long-term effects of GWG on child health (26). Our study addressed that need by using data from a large, ethnically diverse cohort of pregnant women and their infants to examine the influence of maternal prepregnancy BMI and GWG on neonatal adiposity, which is linked to offspring's future risk of obesity (17, 41). We focused on neonatal adiposity to eliminate the influence of postnatal factors that may confound studies linking GWG to childhood obesity. We could not rule out residual confounding by shared genetic factors.

In conclusion, taken together with previously reported associations between GWG and childhood obesity (10–12, 14, 42–45), these findings suggest an obesogenic influence of GWG that may persist into childhood and beyond. Long-term follow-up of participants in Healthy Start and other large cohorts will be important to further our understanding of the developmental origins of obesity, thereby enabling future studies and programs aimed at primordial prevention of obesity and associated chronic diseases.

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