Associations of maternal gestational weight gain with offspring birth size

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ABSTRACT

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Background: Birth size has been associated with lifelong health and disease risk. Better understanding of modifiable risk factors for birth size will help identify at-risk pregnancies and intervention targets. Effects of gestational weight gain (GWG) during specific periods of pregnancy and potential effect modification by offspring gender or maternal pre-pregnancy leisure-time physical activity (LTPA) remain largely unknown.

Methods: We conducted a prospective cohort study of 3,624 mothers and their singleton offspring who sought prenatal care at clinics affiliated with Swedish Medical Center and Tacoma General Hospital, Seattle and Tacoma, WA, 1996-2008. Information on socio-demographic characteristics and medical history was obtained by questionnaire at an average of 15 weeks gestation. GWG (kg) and birth size measures (BSM) including birthweight (BW; g), ponderal index (PI; g/cm^3*100), crown-heel length (CHL; cm), and head circumference (HC; cm) were abstracted from medical records. GWG was characterized as total, early (<20 weeks), and late (≥20 weeks) GWG. "Moderate to vigorous physical activity" was defined as average weekly minutes spent in activity at a metabolic equivalent rating ≥6.We used multivariable linear regression to calculate mean differences and 95% CIs relating total, early, and late GWG to BSM. We tested whether associations of early GWG and late GWG with birth size were quantitatively different using Wald tests. We also tested whether the associations differed by offspring sex or maternal pre-pregnancy LTPA using stratified analyses and interaction terms.

Results: Average total, early, and late GWG were 16.2, 6.8, and 9.5 kg, respectively. We found strong positive associations of total GWG, early GWG, and late GWG with BW. A 1kg increase in total GWG was associated with a 17.2g increase in BW (95% CI 13.8-18.9). A 1kg increase in early GWG was associated with a 14.1g increase (95% CI 10.3-18.0) in BW after adjustment for late GWG. A 1kg increase in late GWG was associated with a 21.0g increase in BW (95% CI 16.7-25.4) after adjustment for early GWG. The association differed for early vs. late GWG (p=0.026). Sex-stratified results for total GWG-BW associations were similar to overall results, but there were sex-specific quantitative differences in early and late GWG-BW associations. Among males, early GWG-BW and late GWG-BW associations were similar (early 15.7, 95% CI 10.0-21.4; late 18.2, 95% CI 12.0-24.5; comparison p=0.579). Among females, a 1kg increase in early GWG was associated with a 12.0g increase in BW (95% CI 6.7-17.2), while a 1kg increase in late GWG was associated with a 24.2g increase in BW (95% CI 18.2-30.3) and these differences were statistically significant (p=0.0042). Sex-GWG (both early and late) interaction terms were not significant however (p=0.549 and 0.354, respectively). Total, early, and late GWG were associated with CHL and HC, but not with PI. There was no evidence that these associations differed by early or late GWG, and the observed associations were not present after adjustment for BW. There was no effect modification of associations of GWG with any of the BSM by LTPA.

Conclusions: Fetuses, particularly female fetuses tend to gain more weight with higher levels of late GWG than with similar higher levels of early GWG. Investigators should consider both period- and sex-specific differences in GWG-BW associations when planning, executing, and interpreting observational and interventional studies.

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I. INTRODUCTION

Birth size, a reflection of intrauterine growth and development, has consistently been associated with health and disease over the life course(1, 2). While extremes of birthweight are well known to be associated with higher risks of obesity, cardiovascular disease, and cancer(3), accumulating evidence also suggests that variation in birthweight within the normal range may be associated with a variety of phenotypes, including cardiovascular disease(4), body composition(5), and intelligence(6). Understanding determinants of birth size and related mechanisms may therefore have broad preventive implications. While risk factors for both macrosomia (including multiparity, advanced maternal age, maternal diabetes, post-term delivery, male sex, and genetic factors)(7) and low birth weight (including maternal smoking, poor nutrition, pre-term delivery, multiple gestation, and genetic factors)(8) have been identified, our understanding of risk factors influencing birthweight across the normal range—particularly modifiable risk factors—and related mechanisms remains incomplete.

Overweight and obesity remain prevalent among women of childbearing age(9). Measures of perinatal maternal size, including pre-pregnancy body-mass index (BMI)(10), and weight gain during pregnancy (GWG)(1), have been associated with offspring birthweight. Associations of GWG with other birth size measures (BSM), such as head circumference (HC), crown-heel length (CHL), and ponderal index (PI), are less rigorously described, as are associations of fetal growth measures with weight gain at specific periods in gestation. Several previous reports suggest that associations of GWG that involve greater gain during the second half of pregnancy may be more strongly associated with BSM, especially BW(11, 12). There is some inconsistency in reported findings however(13). Secondly, sex-specific differences in fetal and placental growth and development patterns, trajectories of growth in response to intrauterine changes, gene-environment interactions, and eventual birth size are well established (14-17). The National Institutes of Health (NIH) has also highlighted the importance of sex-specific differences in recent policy changes(18). To our knowledge, however, sex-specific associations of GWG (including early and late GWG) with birth size have not been systematically explored. Lastly, the contribution of maternal pre- and early pregnancy characteristics and lifestyle factors that may influence associations of maternal GWG with offspring size (**Fig. 1**), such as maternal leisure-time physical activity (LTPA), has not been fully examined.

Using a large pregnancy cohort study, we investigated associations of total, early, and late GWG with birth size measures (BW, PI, CHL, and HC) and differences between early GWG-fetal growth and late GWG-birth size associations. We also examined whether these associations differed by infant sex or maternal pre-pregnancy LTPA.

II. METHODS

Study design and setting:

The study was conducted among participants of the Omega study, a pregnancy cohort study based at the Center for Perinatal Studies at Swedish Medical Center in Seattle, Washington. Study design and protocols have been published previously(19). Briefly, the Omega study was designed to examine metabolic and dietary risk factors of preeclampsia, gestational diabetes, and other pregnancy outcomes. Participants were recruited (1996-2008) from prenatal care clinics affiliated with Swedish Medical Center in Seattle and Tacoma General Hospital in Tacoma, Washington.

Study population:

Pregnant women were eligible to participate in the Omega study if they were ≥18 years old at enrollment, initiated prenatal care prior to 16 weeks of pregnancy, were able to speak and read English, and planned to carry the pregnancy to term and deliver at one of the study hospitals. During the study period, approximately 80% of eligible women who were approached consented to participate and >95% were followed until delivery. All Omega study participants (n=3,624) with singleton pregnancies and complete data on GWG and birth size were included in this analysis. The institutional review boards of Swedish Medical Center and Tacoma General Hospital approved the study, and all study participants provided written informed consent.

Data collection:

At an enrollment visit at approximately 15 weeks gestation, trained interviewers conducted in-person interviews (45-60 minutes in length) to collect data on mothers' age, height, pre-pregnancy weight, socioeconomic characteristics, reproductive and medical histories, tobacco consumption, dietary intake, and physical activity before and during pregnancy. Mothers were followed through delivery, and trained personnel abstracted data on course of pregnancy (e.g., GWG, pregnancy complications) and pregnancy outcomes (e.g., offspring birth characteristics) from maternal and infant medical records. Information on dietary intake during the peri-conception period was obtained at the index visit using food frequency questionnaire data. Information on average weekly recreational physical activity during the year prior to conception, pre-pregnancy LTPA, was collected at the index visit using a structured questionnaire. For each activity, we asked about the frequency and average time spent participating. Each activity was assigned a MET, or metabolic equivalent, rating (a measure of rate of energy expenditure expressed as multiples of the resting metabolic rate) using the Compendium of Physical Activities (https://sites.google.com/site/compendiumofphysicalactivities/). Average weekly time spent in moderate to vigorous LTPA was defined as hours spent in activity at a MET rating ≥3. Additionally, women were categorized as "meeting IOM adult guidelines for leisure-time physical activity" if they reported in engaging in a total of ≥150 minutes per week of activities with a MET rating≥3.

Gestational weight gain:

Total gestational weight gain was calculated as the difference in weight (kilograms) between last recorded maternal weight within 4 weeks of delivery (abstracted from medical records) and self-reported pre-pregnancy weight during the three months prior to conception. Early GWG was calculated by subtracting pre-pregnancy weight from weight at 20 weeks gestation. Late GWG was calculated by subtracting weight at 20 weeks from the last weight before delivery. Additionally, for categorical analyses, weight gain was classified as adequate, inadequate, or excessive based on Institutes of Medicine (IOM) guidelines (**Table 1**). Gestational age was determined using self-reported date of last menstrual period (LMP) and confirmed by the earliest ultrasound, when available, or by physician's best LMP estimate.

Fetal growth measures:

Information on birth weight (grams), ponderal index (g/m^3*100), head circumference (cm), and crown-heel length (cm) at birth, were obtained from medical records. Measurements were obtained immediately after birth and recorded to the nearest 1g and 0.5cm. PI was used in place of body-mass index as a length-normalized estimate of body size. Because it normalizes to the third power of length, it provides more valid comparisons among newborns(20).

Statistical analysis:

We used mean (standard deviation) and number (percent) for continuous and categorical variables, respectively, to describe study population characteristics, both overall and stratified by offspring sex. We used multivariable linear regression to test hypotheses that early and late GWG were independently associated with BW, PI, CHL, and HC. To determine whether associations of early GWG and late GWG with birth size were quantitatively different, we fitted models with each of the four outcome variables (BW, PI, CHL, and HC) and independent terms for early GWG and late GWG. We used a Wald test to examine differences between the coefficients for early GWG and late GWG.

Given evidence suggesting sex-specific differences in growth trajectories and responses to intrauterine growth(14-18), and our hypothesis that early GWG-BSM and late GWG-BSM associations might vary for male and female offspring, we performed sex-stratified analyses. We also used a Wald test to examine differences between the coefficients for early GWG and late GWG in these stratified models. To evaluate the statistical significance of sex-GWG interactions, we fit linear regression models for all birth size measures with and without first-order interaction terms (i.e., terms for total GWG * offspring sex, early GWG * offspring sex, and late GWG * offspring sex). To evaluate the sensitivity of our conclusions to the categorization of GWG, we further modeled the expected change in offspring size for women with excessive or inadequate GWG for pre-pregnancy size, using IOM guidelines, and used a likelihood ratio test to compare the equivalence of models with and without first-order interaction terms for category of GWG * offspring sex. Lastly, to address the possibility of effect modification by LTPA, in multivariable linear regression models, we used a likelihood-ratio test to compare the equivalence of models with and without interaction terms between LTPA and total/early/late GWG.

All models adjusted for maternal age (years), maternal pre-pregnancy body-mass index (kg/m^2), maternal height (m), nulliparous status (yes/no), marital status (married/unmarried), race (white/other), <12 years of education (yes/no), presence of any maternal hypertensive disorder including chronic hypertension, pregnancy-induced hypertension, or pre-eclampsia (yes/no), presence of maternal glucose metabolism disorder (yes/no), maternal smoking during pregnancy (yes/no), and offspring sex and gestational age at delivery (weeks).

In sensitivity analyses, we controlled for maternal dietary factors including total maternal caloric intake in the week prior to interview and percent of calories from fat (data not shown). To check for the possibility of influential outliers, we estimated delta-betas from the regression equations. To address the possibility of non-linear GWG-BSM associations, we repeated all analyses using multinomial logistic regression to estimate the relative risk of giving birth to an infant in a higher (>1SD above the mean) or lower (>1SD below the mean) birth size category across categories of GWG (>1SD above the mean, within 1SD of the mean, and >1SD below the mean). To further address the possibility of a non-linear relationship between GWG and birthweight, we fit models with quadratic total, early, and late GWG terms, as well as linear spline-based models with knots at quartiles of total, early, and late GWG.

Analyses were performed using Stata 12.1 (College Station, TX). For all tests, a two-sided α of 0.05 was used.

III. RESULTS

The cohort comprised predominantly married non-Hispanic white women (**Table 2**). They were 32.6 years old at time of enrollment, on average. Mean pre-pregnancy BMI was 23.7 kg/m^2. Average total, early (<20 weeks gestation), and late GWG (≥20 weeks gestation) were 16.2, 6.8, and 9.5 kg, with 54% of women gaining in excess of IOM guidelines. In general, subjects were physically active, with 91% reporting engaging in some type of LTPA prior to pregnancy, and 67% met IOM guidelines for physical activity in adults. Average gestational age at delivery was 39 weeks, and 51% of offspring were male. Fetal growth measures were normally distributed. Mean BW was 3,443g (3,513g for males and 3,382g for females). Mean PI was 2.7g/cm^3*100. Mean HC was 35cm, and mean CHL was 51cm.

Overall, we found strong positive associations of total, early, and late GWG with BW, HC, and CHL, but not PI (**Table 3**). A 1kg increase in total GWG was associated with a 17.2g mean increase in BW (95% CI 13.8-18.9). A 1kg increase in early GWG was associated with a 14.1g increase (95% CI 10.3-18.0) in BW after adjustment for late GWG. A 1kg increase in late GWG was associated with a 21.0g increase in BW (95% CI 16.7-25.4) after adjustment for early GWG. The association differed for early vs. late GWG (p=0.026).

Sex-stratified results for total GWG were not different in male offspring (17.1, 95% CI 13.1-21.2) versus female offspring (17.1, 95% CI 14.5-20.9). Among males, early GWG-BW and late GWG-BW associations were similar (early 15.7, 95% CI 10.0-21.4; late 18.2, 95% CI 12.0-24.5; p for comparison=0.579). In contrast, among females, a 1kg increase in early GWG was associated with a 12.0g increase in BW (95% CI 6.7-17.2), while a 1kg increase in late GWG was associated with a 24.2g increase in BW (95% CI 18.2-30.3; p for comparison=0.0042). Terms for early and late GWG interactions with offspring sex were not significant (p-values 0.549 and 0.354, respectively), however, indicating that there was no statistical evidence that independent associations of early or late GWG with any BSM depended on offspring sex (**Table 2**).

Overall, total, early, and late GWG were associated with HC and CHL, but not PI (**Table 3**). A 1kg increase in total, early, or late GWG was associated with 0.038-0.042cm higher HC and 0.052-0.070 cm higher CHL (all p-values <0.002). Results were generally similar in sex-stratified models with no differences observed between males and females in the GWG-HC/CHL associations, although early GWG-CHL associations among male offspring were not statistically significant. All the associations became non-significant after adjustment for BW. Further, tests for differences between early GWG-HC/CHL and late GWG-HC/CHL associations were not significant.

Findings from analyses using alternate categorizations of GWG, first into excessive, adequate, or inadequate (**Table 4a**) and then into quartiles of early and late GWG (**Table 4b, 4c**) were similar to those reported above. Further, there was no statistical evidence for effect modification by LTPA of any of the GWG-BSM associations (**Table 5**).

In sensitivity analyses, there was some evidence that associations of early GWG and BW might be non-linear. There were, however, very few values at the extremes of the BW distribution (**Table 6** and **Figure 2**). Scatter plots of studentized residuals vs. total, early, and late GWG (not shown) showed no trends. Results from multinomial logistic regression models with categorized BSM (data not shown) were similar to results from our primary models. Results were also not quantitatively different when we controlled for pre-pregnancy maternal caloric intake, percent calories from fat, and LTPA (data not shown).

IV. DISCUSSION

We found strong associations of total GWG, early GWG, and late GWG with BW, HC, and CHL, but not PI. Associations of GWG with HC and CHL were not statistically significant after adjustment for BW. While we did not observe statistically significant differences in independent associations of early GWG and BW or late GWG and BW by offspring sex (p-values 0.549 and 0.354 respectively), the early GWG-BW association was quantitatively different from the late GWG-BW association among female offspring (12.0g/kg early GWG, 24.2g/kg late GWG, p-value for difference 0.0042) but not males (15.7g/kg early GWG, 18.2g/kg late GWG, p-value for difference 0.5787). We did not observe any effect modification of early or late GWG-BSM associations by pre-pregnancy LTPA.

Reports comparing early and late GWG have suggested that higher levels of late GWG are associated with higher BW compared to early GWG(11-13). There are, however, few studies available, and the results are not entirely consistent. In an African cohort, GWG after 32 weeks gestation was more strongly associated with BW than gain between 7 and 32 weeks in lean women(11). Among young women in 1950s Scotland, inadequate GWG between 20 to 30 and 30 to 36 weeks was associated with higher rates of low birth weight than inadequate gain between 13 and 20 weeks(12). Conversely, in a cohort similar to ours, Davenport and co-authors reported that mothers who had weight gain patterns with *excess* GWG prior to 16-20 weeks had greater BW than mothers with excess GWG after 16-20 weeks as well as 50% higher odds of neonatal body fat >14%(13). Other studies have compared associations of maternal GWG across trimesters with BSM. Several authors have reported trends toward a stronger association of second-trimester GWG with BW than gain in the first or third trimester(21-25). In a cohort of healthy, non-obese white women, Abrams and co-authors observed that patterns of GWG that involved low second-trimester gain were associated with lower average BW(21) than patterns that did not involve low second-trimester gain. Similarly, in 1980s Alabama, black and white mothers at high risk of intrauterine growth restriction had offspring with lower mean BW when they had low GWG by IOM guidelines during the second trimester(22) but not when the pattern did not involve low second-trimester gain. In a number of studies, authors have also reported quantitatively stronger second-trimester GWG-BW associations that did not reach statistical significance(23, 25). To our knowledge, previous studies have not evaluated offspring sex-specific associations or effect modification by offspring sex or pre-pregnancy LTPA.

There are a number of factors that could be expected to contribute to heterogeneity of results. As illustrated above, authors have variably compared early-late gain differences or differences in GWG across trimesters. Definitions of "early" and "late," as well as trimester cutpoints also vary across study populations. Differences in study population characteristics (e.g., pre-pregnancy overweight(26)) could also contribute to differences in findings across studies and to generalizability of findings. In our population, roughly 60% gained in excess of IOM guidelines, similar to current weight patterns among reproductive-age American women. The probability of misclassification and measurement error were highly variable across these diverse cohort designs, with prospectively collected first-trimester weights available in some cohorts, while in others, the first objectively measured weights were recorded at nearly 18 weeks gestation. There was also heterogeneity in BSM across the populations (e.g., most used BW, but others chose to emphasize fetal adiposity(13)). Finally, there was considerable variability in analytic approach (including formal testing of differences between early GWG-BW and late GWG-BW associations) and study power.

In the current study, the pattern of smaller gains in BW for corresponding increases in early GWG compared to similar increases in late GWG was observed in female offspring (12.0 g/kg early GWG and 24.2g/kg late GWG), but not male offspring (15.7 g/kg and 18.2g/kg, respectively). This observation is supported by mechanistic evidence of metabolic and hormonal changes occurring in the second half of pregnancy that may be more pronounced among female fetuses than males. Compared with women who are pregnant with male fetuses, women who were pregnant with female fetuses have higher serum placental growth hormone in the third trimester(27) and higher levels of insulin-like growth factor 1 at birth(28), two important regulators of fetal growth. Sex-specific differences in placental response to maternal factors have also been reported. For example, female placentas exhibit higher levels of expression of genes involved in placental growth(29). Greater placental weight is also associated with increases in maternal fasting glucose among females but not males(30). The female fetal growth pattern seems to mirror the maternal trajectory, in which the bulk of weight is gained in the second half of gestation. Sex dimorphism has also been seen in response to pathological changes that may have gestational-age–dependent effects on the intrauterine environment(31). For example, in mothers with mild pre-eclampsia, which is clinically manifest in late pregnancy, male babies reach normal size, while female babies are smaller(14). Taken together, these observations suggest that effects of maternal energy balance (such as maternal GWG) at different points in the pregnancy may differ between male and female infants because of sex-specific sensitivities across gestational ages. Recent NIH policy changes have highlighted growing awareness that females and males respond differently to chemical and microbial stressors via mechanisms that are both hormonally independent and hormonally mediated(18). Future studies further investigating mechanisms underlying these sex-specific effects are warranted.

GWG-HC and GWG-CHL associations appeared to remain stable across the course of pregnancy. Comparison of early GWG-PI and late GWG-PI associations in female offspring did show a trend toward smaller gains in PI for similar increases for early compared to late GWG, but it did not reach statistical significance (p=0.0718). The weight of the fetus at term (approximated by BW) makes up roughly 20-30 percent of GWG. It is therefore not surprising that associations with measures such as HC and CHL, which do not include a component tightly correlated with GWG, were not significant compared with GWG-birth size associations. Further, in the case of both HC and CHL, quantitative differences in our sample from the smallest to the largest infants may have been so small that we were unable to detect a difference in early/late GWG patterns. Lack of power may also explain the fact that our statistical tests of effect modification by sex were not significant, despite the fact that we saw evidence that early GWG-BW associations were quantitatively different than late GWG-BW in female offspring but not male. We cannot exclude the possibility of type I error, however, especially given the multiple statistical tests we performed. It will be important to replicate these findings in other cohorts.

This study is the largest, to our knowledge, to demonstrate that GWG after 20 weeks has a different, and likely stronger, association with BW, than GWG before 20 weeks. It is also the first to demonstrate sex-specific differences in the association. These findings are important in understanding early life determinants of offspring health across the life course. This study has several strengths, including the prospective study design. Maternal weight was measured several times across the course of pregnancy, and women were followed prospectively until delivery. Other strengths include the large sample size and detailed information on potential confounders. Several limitations of our study also deserve mention. We used self-reported retrospective measures of both pre-pregnancy weight and LTPA. Women tend to underestimate pre-pregnancy weight, and this behavior may be more exaggerated in women with greater pre-pregnancy BMI; however, reported pre-pregnancy weights rarely differ from measured values by more than 10 percent even in the higher BMI categories(32, 33). We also do not anticipate this to bias sex-specific differences in associations. Another limitation of our study is our inability to estimate fetal weight contributions to measures of early and late GWG. Our cohort was predominantly physically active and non-obese. Pre-pregnancy LTPA was common and frequent in this cohort, which may have reduced variation and contributed to lack of statistical power in our study to evaluate potential effect modification. Similar studies are needed in more diverse study populations to ensure generalizability of findings.

In sum, our findings indicate that BW increases were exaggerated during late GWG among female offspring. Future studies with detailed measures of change in maternal body composition and fetal adiposity may help elucidate underlying mechanisms behind the observed associations and sex-specific differences. Further, potential implications of the observed associations on chronic disease risk in postnatal life are important targets of future research. A better understanding of these associations and mechanisms can be translated into improved clinical practice, helping clinicians identify at-risk pregnancies and guiding GWG-based interventions.

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Table 1. Institutes of Medicine weight gain recommendations for pregnancy

Pre-pregnancy Body Mass Index (kg/m^2)	Recommended Range of Total Weight (kg)	Recommended Rates of Weight Gain* in the Second and Third Trimesters (kg/wk)
<18.5	12.5-18	0.5
18.5–24.9	11.5-16	0.4
25–29.9	7-11.5	0.3
>=30	5-9	0.2

*Assumes a 0.5–2-kg weight gain in the first trimester
Modified from Institutes of Medicine (US). Weight gain during pregnancy: Reexamining the guidelines. Washington, DC. National Academies Press; 2009. ©2009 National Academy of Sciences(1)

Table 2. Characteristics of mother-singleton offspring pairs in the Omega birth cohort, overall and stratified by offspring sex (n = 3621)

	All n = 3621	**Male** n = 1840	**Female** n = 1781
Maternal characteristics			
Maternal age, years (SD)	32.6 (4.6)	32.6 (4.6)	32.5 (4.5)
Pre-pregnancy BMI, kg/m^2 (SD)	23.7 (5.1)	23.7 (5.1)	23.8 (5.0)
Maternal height, meters (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Nulliparous % (n)	39 (1414)	38 (706)	40 (708)
Married, % yes (n)	85 (3247)	86 (1586)	86 (1539)
Less than 12 years of education, % yes (n)	4 (141)	4 (71)	4 (61)
Race			
Non-Hispanic white, % (n)	86 (3251)	85 (1561)	86 (1532)
African-American, % (n)	2 (74)	2 (37)	2 (34)
Asian, % (n)	8 (286)	8 (150)	7 (121)
Hispanic, % (n)	2 (65)	2 (34)	2 (29)
Other, % (n)	3 (110)	3 (53)	3 (56)
Smoked during pregnancy, % yes (n)	6 (214)	6 (107)	6 (97)
Maternal glucose metabolism disorder, % yes (n)	6.5 (234)	6.4 (118)	6.5 (116)
Gestational diabetes, % yes (n)	5 (188)	5 (94)	5 (93)
Pre-existing diabetes, % yes (n)	1 (56)	1 (25)	1 (23)
Maternal hypertensive disorder, % yes (n)	18.6 (668)	18.6 (339)	18.7 (329)
Chronic hypertension, % yes (n)	5 (185)	4 (77)	5 (95)
Pregnancy-induced hypertension, % yes (n)	12 (432)	13 (239)	11 (193)
Pre-eclampsia, % yes (n)	3 (109)	2 (42)	4 (67)
GWG variables			
Total gestational weight gain, kg (SD)	16.2 (5.7)	16.5 (5.5)	15.9 (5.9)
Total GWG by IOM category, kg (SD)			
Inadequate, % (n)	14 (510)	10 (184)	12 (218)
Adequate, % (n)	32 (1202)	31 (569)	34 (608)
Excessive, % (n)	54 (2034)	59 (1067)	53 (943)
Early GWG, kg (SD)*	6.8 (3.9)	6.8 (3.7)	6.7 (4.0)
Late GWG, kg (SD)**	9.5 (3.7)	9.7 (3.7)	9.2 (3.7)
Pre-pregnancy physical activity variables			
Median minutes of moderate or greater pre-pregnancy LTPA (IQR)	228 (111-388)	224 (111-388)	231 (111-390)
% meeting IOM adult guidelines of >150 minutes of moderate-intensity activity/week	67 (2231)	67 (1139)	67 (1092)
Offspring characteristics			
Gestational age, weeks (SD)	39 (2)	39 (2)	39 (2)
Sex, % male (n)	51 (1840)	—	—
Outcome measures			
Birthweight, grams (SD)	3443 (576)	3513 (570)	3382 (540)
Ponderal index, g/cm^3 *100 (SD)	2.7 (1.3)	2.7 (1.0)	2.7 (1.5)
Head circumference (cm)	35 (3)	35 (2)	34 (2)
Length (cm)	51 (4)	51 (3)	50 (3)

* Early GWG was calculated by subtracting pre-pregnancy weight from weight at 20 weeks gestation
** Late GWG was calculated by subtracting weight at 20 weeks from the last weight before delivery

Table 3. Offspring birth size in relation to 1-kg increases in total, early, and late gestational weight gain (GWG), overall and stratified by offspring sex

	All Subjects n = 3621		**Male** n = 1840		**Female** n = 1781		**Interaction model**
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	p for interaction*
Birthweight, g							
Total GWG	17.2 (14.5-19.9)	<0.0001	17.1 (13.1-21.2)	<0.0001	17.1 (14.5-20.9)	<0.0001	0.973
Early GWG	14.1 (10.3-18.0)	<0.0001	15.7 (10.0-21.4)	<0.0001	12.0 (6.7-17.2)	<0.0001	0.549
Late GWG	21.0 (16.7-25.4)	<0.0001	18.2 (12.0-24.5)	<0.0001	24.2 (18.2-30.3)	<0.0001	0.354
Wald test (early vs. late)**	4.96	0.026	0.31	0.5787	8.22	0.0042	
Ponderal index, g/cm^3 * 100							
Total GWG	0.005 (-0.0001-0.010)	0.054	0.009 (-0.0004-0.019)	0.060	0.0009 (-0.004-0.005)	0.682	0.376
Total GWG, adjusted for BW	-0.0002 (-0.006-0.005)	0.937	0.005 (-0.006-0.016)	0.390	-0.005 (-0.010-0.001)	0.053	
Early GWG	-0.0005 (-0.008-0.008)	0.886	0.007 (-0.003-0.016)	0.161	-0.007 (-0.018-0.004)	0.187	0.062
Late GWG	0.012 (0.0002-0.024)	0.047	0.012 (-0.008-0.032)	0.224	0.012 (0.00004-0.024)	0.049	0.721
Wald test (early vs. late)**	2.26	0.1331	0.22	0.6408	3.25	0.0718	
Head circumference, cm							
Total gestational weight gain	0.040 (0.25-0.054)	<0.0001	0.045 (0.021-0.070)	<0.0001	0.034 (0.018-0.051)	<0.0001	0.636
Total GWG, adjusted for BW	0.006 (-0.008-0.019)	0.413	0.01 (-0.013-0.034)	0.373	0.001 (-0.013-0.016)	0.861	
Early weight gain	0.038 (0.014-0.062)	0.002	0.052 (0.010-0.095)	0.016	0.024 (0.003-0.047)	0.047	0.254
Late weight gain	0.042 (0.021-0.063)	<0.0001	0.040 (0.009-0.070)	0.011	0.047 (0.018-0.76)	0.001	0.483
Wald test (early = late)**	0.06	0.8110	0.18	0.6725	1.33	0.2487	
Crown heel length, cm							
Total GWG	0.060 (0.042-0.078)	<0.0001	0.050 (0.022-0.086)	0.001	0.069 (0.046-0.092)	<0.0001	0.634
Total GWG, adjusted for BW	0.009 (-0.007-0.025)	0.292	-0.003 (-0.028-0.022)	0.818	0.020 (-0.0008-0.040)	0.06	
Early GWG	0.052 (0.023-0.080)	<0.0001	0.039 (-0.05-0.082)	0.079	0.062 (0.026-0.098)	0.001	0.434
Late GWG	0.070 (0.042-0.097)	<0.0001	0.059 (0.018-0.100)	0.005	0.079 (0.04-0.12)	<0.0001	0.992
Wald test (early vs late)**	0.69	0.4072	0.4	0.5261	0.36	0.5504	

Early GWG was calculated by subtracting pre-pregnancy weight from weight at 20 weeks gestation. Late GWG was calculated by subtracting weight at 20 weeks from the last weight before delivery.

Models adjust for maternal age, maternal pre-pregnancy BMI, maternal height, nulliparous status, marital status, race, <12 years of education, presence of maternal hypertensive disorder, presence of maternal glucose metabolism disorder, maternal smoking status, and offspring sex and gestational age at delivery

* p-value for multiplicative interaction taken from model specified above, weight gain modeled continuously

Table 4a. Effect modification of the association between excess *total* gestational weight gain and offspring birth size by offspring sex (n = 3365)

	Expected difference in offspring size for women with too little or too much GWG by IOM guidelines		
	Adequate	Inadequate gain	Excessive gain
Birthweight, g			
Male	Ref	-100 (-168, -31)	142 (100, 185)
Female	Ref	-178 (-140, -17)	174 (133, 216)
LR test chi-squared (p)*			1.08 (0.5832)
Ponderal index, g/cm³ * 100			
Male	Ref	-0.05 (-0.15, 0.05)	0.06 (-0.04, 0.16)
Female	Ref	-0.06 (-0.24, 0.11)	0.00 (-0.18, 0.18)
LR test chi-squared (p)			0.42 (0.8116)
Head circumference, cm			
Male	Ref	-0.4 (-0.8, 0.0)	0.1 (-0.1, 0.3)
Female	Ref	0.0 (-0.4, 0.5)	0.4 (0.3, 0.6)
LR test chi-squared (p)			5.91 (0.0521)
Length, cm			
Male	Ref	-0.3 (-0.8, 0.2)	0.4 (0.1, 0.7)
Female	Ref	-0.1 (-0.6, 0.4)	0.9 (0.5, 1.1)
LR test chi-squared (p)			3.78 (0.1509)

* Chi-squared and p-value from likelihood ratio test comparing model with term for interaction between IOM GWG category and offspring sex to model without interaction term

Table 4b. Effect modification of the association between *early* gestational weight gain and offspring birth size by offspring sex (n = 3319)

	Expected difference in offspring size by quartile of early GWG			
	1	2	3	4
Birthweight, g				
Male	Ref	61 (5, 117)	113 (60, 166)	132 (78,185)
Female	Ref	60 (4, 117)	106 (52, 161)	146 (91, 201)
LR test chi-squared (p)*				0.32 (0.9568)
Ponderal index, g/cm³ * 100				
Male	Ref	-0.1 (-0.2, 0.2)	0.1 (0.0, 0.3)	0.0 (-0.1, 0.2)
Female	Ref	0.2 (0.0, 0.4)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.2)
LR test chi-squared (p)*				8.33 (0.0398)
Head circumference, cm				
Male	Ref	0.0 (-0.3, 0.2)	0.2 (0.0, 0.5)	0.3 (0.0, 0.5)
Female	Ref	-0.1 (-0.4, 0.2)	0.1 (-0.1, 0.4)	0.2 (-0.1, 0.5)
LR test chi-squared (p)*				0.28 (0.9631)
Length, cm				
Male	Ref	0.3 (-0.1, 0.6)	0.1 (-0.3, 0.4)	0.3 (-0.1, 0.7)
Female	Ref	0.2 (-0.2, 0.6)	0.5 (-0.2, 0.9)	0.7 (0.3, 1.0)
LR test chi-squared (p)*				5.44 (0.1422)

* Chi-squared and p-value from likelihood ratio test comparing model with term for interaction between quartile of early GWG and offspring sex to model without interaction term

Table 4c. Effect modification of the association between *late* gestational weight gain and offspring birth size by offspring sex (n = 3319)

	Expected difference in offspring size by quartile of late GWG			
	1	2	3	4
Birthweight, g				
Male	Ref	86 (29, 143)	116 (61, 171)	193 (139, 248)
Female	Ref	107 (52, 163)	123 (68, 177)	226 (171, 281)
LR test chi-squared (p)*				0.89 (0.8282)
Ponderal index, g/cm³ * 100				
Male	Ref	0.03 (-0.16, 0.21)	0.01 (-0.17, 0.19)	0.08 (-0.10, 0.26)
Female	Ref	0.08 (-0.11, 0.26)	0.13 (-0.05, 0.30)	0.18 (0.00, 0.36)
LR test chi-squared (p)*				1.07 (0.7854)
Head circumference, cm				
Male	Ref	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.4)	0.4 (0.1, 0.6)
Female	Ref	0.4 (0.1, 0.6)	0.4 (0.2, 0.7)	0.5 (0.3, 0.8)
LR test chi-squared (p)*				2.16 (0.5400)
Length, cm				
Male	Ref	0.2 (-0.2, 0.6)	0.4 (0.0, 0.8)	0.7 (0.3, 1.1)
Female	Ref	0.0 (-0.3, 0.4)	0.4 (0.0, 0.8)	0.6 (0.2, 1.0)
LR test chi-squared (p)*				0.55 (0.9070)

* Chi-squared and p-value from likelihood ratio test comparing model with term for interaction between quartile of late GWG and offspring sex to model without interaction term

Table 5. Effect modification of the association between IOM categories of gestational weight gain (GWG) and offspring birth size by pre-pregnancy leisure-time physical activity, overall and stratified by offspring sex

	Expected difference in offspring size for women with too little or too much GWG by IOM guidelines								
	Overall			***Boys***			***Girls***		
	Adequate	Inadequate gain	Excessive gain	Adequate	Inadequate gain	Excessive gain	Adequate	Inadequate gain	Excessive gain
Birthweight, g									
LTPA quartile 1	Ref	-32 (-123, 59)	162 (101, 222)	Ref	-70 (-206, 67)	112 (22, 202)	Ref	2 (-119, 123)	203 (-121, 287)
LTPA quartile 2	36 (-105, 32)	-20 (-117, 78)	196 (133, 258)	-41 (-141, 58)	-45 (-186, 97)	153 (67, 240)	-43 (-139, 53)	11 (-124, 46)	241 (151, 331)
LTPA quartile 3	-21 (-88, 46)	-149 (-249, 48)	127 (68, 187)	-39 (-140, 62)	-212 (-356, -67)	106 (19, 194)	-7 (-96, 81)	-82 (-222, 58)	147 (66, 227)
LTPA quartile 4	-21 (-90, 48)	-142 (-243, -42)	150 (89, 212)	-38 (-141, 64)	-44 (-209, 119)	177 (88, 265)	-12 (-105, 81)	-202 (-328, 75)	119 (34, 205)
LR test p*			0.3231			0.5840			0.1820
Ponderal index, g/cm³ *100									
LTPA quartile 1	Ref	0.0 (-0.3, 0.3)	0.0 (-0.1, 0.2)	Ref	0.0 (-0.2, 0.2)	0.1 (-0.1, 0.2)	Ref	0.0 (-0.5, 0.5)	0.0 (-0.3, 0.3)
LTPA quartile 2	0.0 (-0.2, 0.2)	0 (-0.3, 0.3)	0.1 (-0.1, 0.3)	0.1 (0.0, 0.2)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.1)	-0.1 (-0.5, 0.3)	0.1 (-0.1, 0.6)	0.3 (-0.1, 0.6)
LTPA quartile 3	0.1 (-0.1, 0.3)	-0.2 (-0.5, 0.1)	-0.1 (-0.3, 0.1)	0.0 (-0.1, 0.2)	0.0 (-0.2, 0.1)	-0.1 (-0.3, 0.1)	0.2 (-0.2, 0.5)	-0.3 (-0.9, 0.3)	-0.2 (-0.5, 0.1)
LTPA quartile 4	0.1 (-0.1, 0.3)	0 (-0.3, 0.3)	0 (-0.2, 0.2)	0.1 (0.0, 0.3)	0.1 (-0.1, 0.2)	-0.1 (-0.4, 0.1)	0.0 (-0.4, 0.4)	0.0 (-0.5, 0.6)	0.0 (-0.4, 0.3)
LR test p*			0.8358			0.8250			0.6039
Head									
LTPA quartile 1	Ref	-0.1 (-0.1, 0.4)	0.3 (0.0, 0.6)	Ref	-0.1 (-0.8, 0.7)	0.2 (-0.3, 0.6)	Ref	0.0 (-0.6, 0.6)	0.4 (0.0, 0.8)
LTPA quartile 2	0.0 (-0.4, 0.3)	0.0 (-0.5, 0.4)	0.3 (0.0, 0.6)	0.2 (-0.3, 0.8)	-0.1 (-0.9, 0.6)	0.0 (-0.5, 0.5)	-0.3 (-0.7, 0.2)	0.1 (-0.5, 0.7)	0.6 (0.2, 1.0)
LTPA quartile 3	0.0 (-0.3, 0.4)	-0.4 (-1.0, 0.1)	0.2 (-0.1, 0.5)	0.2 (-0.4, 0.7)	-0.6 (-1.4, 0.2)	0.1 (-0.3, 0.6)	-0.1 (-0.5, 0.3)	-0.3 (-0.9, 0.4)	0.3 (-0.1, 0.7)
LTPA quartile 4	0.2 (-0.2, 0.5)	-0.1 (-0.7, 0.4)	0.3 (0.0, 0.6)	0.7 (0.1, 1.2)	-0.9 (-1.8, 0.0)	0.0 (-0.4, 0.5)	-0.3 (-0.7, 0.1)	0.5 (-0.1, 1.1)	0.5 (0.1, 0.9)
LR test p*			0.9562			0.7705			0.6723
Length, cm									
LTPA quartile 1	Ref	-0.1 (-0.7, 0.5)	0.6 (0.1, 1.0)	Ref	-0.4 (-1.3, 0.5)	0.1 (-0.5, 0.7)	Ref	0.2 (-0.7, 1.1)	0.9 (0.3, 1.5)
LTPA quartile 2	-0.3, (-0.8, 0.1)	0.0 (-0.7, 0.6)	0.8 (0.4, 1.2)	-0.6 (-1.2, 0.1)	0.0 (-0.9, 0.9)	0.7 (0.1, 1.3)	-0.1 (-0.8, 0.6)	0.0 (-0.9, 1.0)	0.8 (0.2, 1.5)
LTPA quartile 3	-0.1 (-0.6, 0.3)	-0.3 (-1.0, 0.3)	0.4 (0.0, 0.9)	-0.3 (-1.0, 0.3)	-0.8 (-1.7, 0.2)	0.1 (-0.5, 0.7)	0.1 (-0.6, 0.7)	0.1 (-1.0, 1.1)	0.8 (0.2, 1.3)
LTPA quartile 4	-0.4 (-0.9, 0.0)	-0.5 (-1.2, 0.2)	0.8 (0.4, 1.3)	-0.6 (-1.2, 0.1)	0.2 (-0.9, 1.3)	0.6 (0.1, 1.2)	-0.4 (-1.1, 0.2)	-0.9 (-1.8, 0)	1.1 (0.5, 1.7)
LR test p*			0.6237			0.6059			0.4462

* p-value from likelihood ratio test comparing model with Institutes of Medicine GWG category * quartile of LTPA interaction term to model without interaction term

Table 6. Evidence for non-linearity of associations of total, early-, and late-pregnancy GWG with offspring birthweight in grams, overall and stratified by offspring sex

	Quadratic models*			Spline models**					
	Total	*Early*	*Late*	*Total*	*p-value*	*Early*	*p-value*	*Late*	*p-value*
Overall	**0.027**	**0.001**	0.395	**3.15**	**0.024**	2.48	0.0595	1.1	0.3481
Only boys	0.988	0.19	0.771	0.87	0.4566	0.75	0.5197	1.05	0.3672
Only girls	**0.002**	**0.001**	0.46	**4.17**	**0.0059**	**2.76**	**0.0409**	0.43	0.7342

* p-values from quadratic terms added one at a time to primary models

** Wald test from linear spline model (quartiles of total, early, or late GWG—overall and sex-specific)

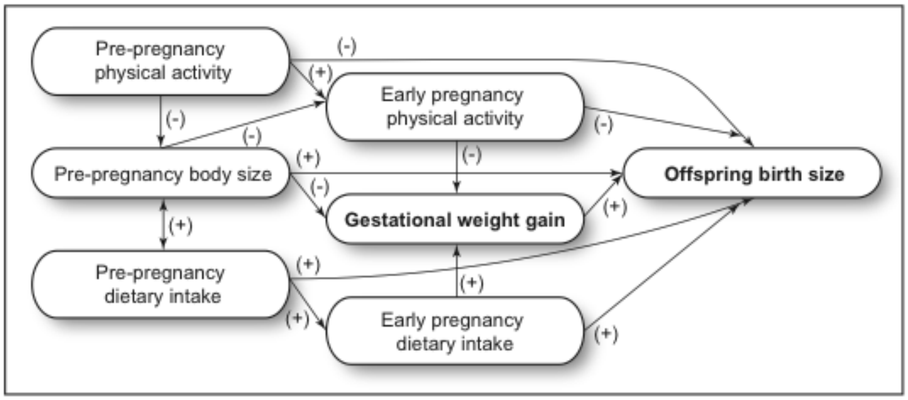

Fig. 1. Model of associations of maternal body size, maternal leisure-time physical activity before and during early pregnancy, and offspring birth size. Summary of how maternal physical activity and body size might influence offspring body size at birth.

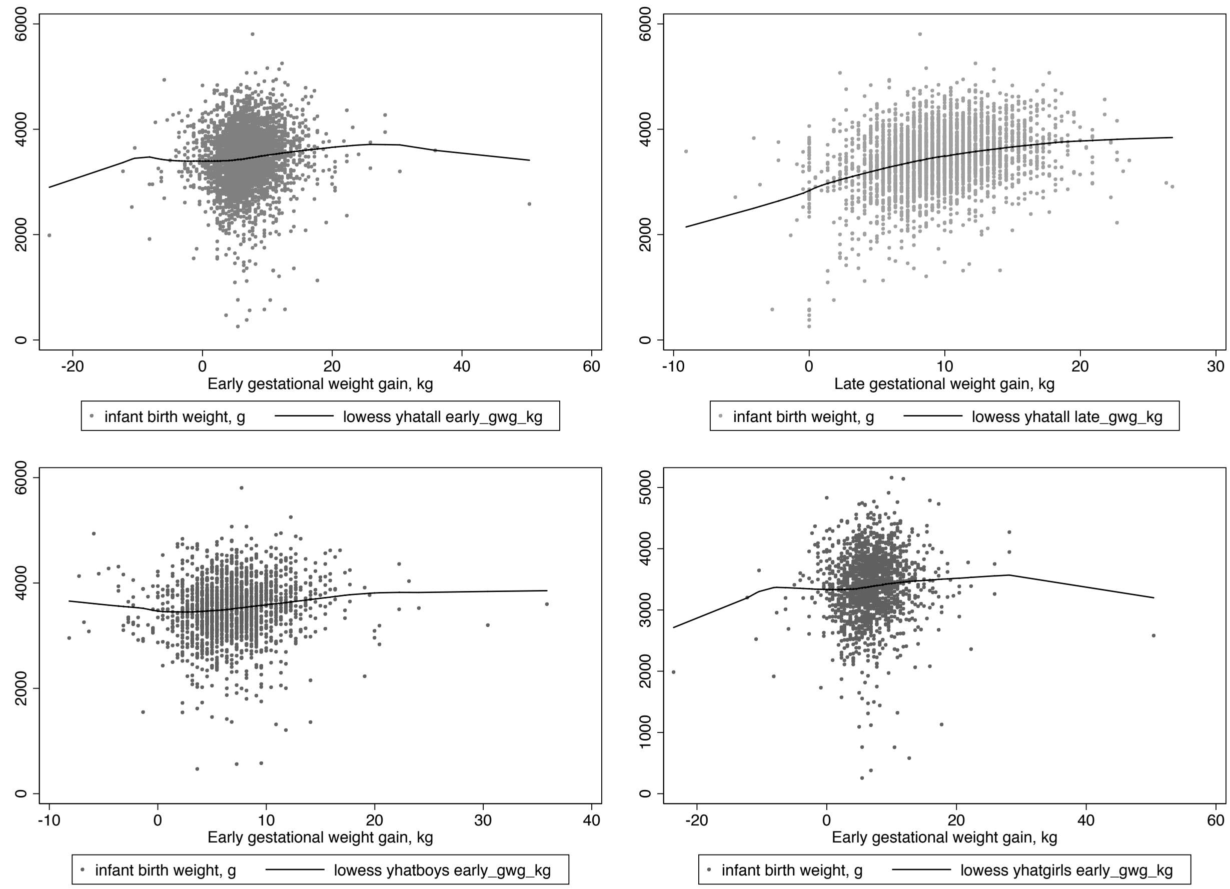

Fig 2. Scatter plots of gestational weight gain versus offspring birth weight. (a) early GWG vs BW, overall; (b) late GWG vs. BW, overall; (c) early GWG vs. BW, boys only; (d) late GWG vs. BW, girls only with lowess plot of fitted values from corresponding primary model overlaid