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Journal

American Journal of Obstetrics and Gynecology, 217(3)

ISSN

0002-9378

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Publication Date

2017-09-01

DOI

10.1016/j.ajog.2017.05.013

OBSTETRICS

Patterns of gestational weight gain and birthweight outcomes in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies—Singletons: a prospective study

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BACKGROUND: Inadequate or excessive total gestational weight gain is associated with increased risks of small- and large-for-gestational-age births, respectively, but evidence is sparse regarding overall and trimester-specific patterns of gestational weight gain in relation to these risks. Characterizing the interrelationship between patterns of gestational weight gain across trimesters can reveal whether the trajectory of gestational weight gain in the first trimester sets the path for gestational weight gain in subsequent trimesters, thereby serving as an early marker for at-risk pregnancies.

OBJECTIVE: We sought to describe overall trajectories of gestational weight gain across gestation and assess the risk of adverse birthweight outcomes associated with the overall trajectory and whether the timing of gestational weight gain (first vs second/third trimester) is differentially associated with adverse outcomes.

STUDY DESIGN: We conducted a secondary analysis of a prospective cohort of 2802 singleton pregnancies from 12 US prenatal centers (2009 through 2013). Small and large for gestational age were calculated using sex-specific birthweight references <5th, <10th, or ≥90th percentiles, respectively. At each of the research visits, women's weight was measured following a standardized anthropometric protocol. Maternal weight at antenatal clinical visits was also abstracted from the prenatal records. Semiparametric, group-based, latent class, trajectory models estimated overall gestational weight gain and separate first- and second-/third-trimester trajectories to assess tracking. Robust Poisson regression was used to estimate the relative risk of small- and large-for-gestational-age outcomes by the probability of trajectory membership. We tested whether relationships were modified by prepregnancy body mass index.

RESULTS: There were 2779 women with a mean of 15 (SD 5) weights measured across gestation. Four distinct gestational weight gain trajectories were identified based on the lowest Bayesian information criterion value, classifying 10.0%, 41.8%, 39.2%, and 9.0% of the population from lowest to highest weight gain trajectories, with an inflection at 14 weeks. The average rate in each trajectory group from lowest to highest for 0-<14 weeks was −0.20, 0.04, 0.21, and 0.52 kg/wk and for 14-39 weeks was 0.29, 0.48, 0.63, and 0.79 kg/wk, respectively; the second lowest gaining trajectory resembled the Institute of Medicine recommendations and was designated as the reference with the other trajectories classified as low, moderate-high, or high. Accuracy of assignment was assessed and found to be high (median posterior probability 0.99, interquartile range 0.99-1.00). Compared with the referent trajectory, a low overall trajectory, but not other trajectories, was associated with a 1.55-fold (95% confidence interval, 1.06−2.25) and 1.58-fold (95% confidence interval, 0.88−2.82) increased risk of small-for-gestational-age <10th and <5th, respectively, while a moderate-high and high trajectory were associated with a 1.78-fold (95% confidence interval, 1.31−2.41) and 2.45-fold (95% confidence interval, 1.66−3.61) increased risk of large for gestational age, respectively. In a separate analysis investigating whether early (<14 weeks) gestational weight gain tracked with later (≥14 weeks) gestational weight gain, only 49% (n = 127) of women in the low first-trimester trajectory group continued as low in the second/third trimester, and had a 1.59-fold increased risk of small for gestational age; for the other 51% (n = 129) of women without a subsequently low second-/third-trimester gestational weight gain trajectory, there was no increased risk of small for gestational age (relative risk, 0.75; 95% confidence interval, 0.47−1.38). Prepregnancy body mass index did not modify the association between gestational weight gain trajectory and small for gestational age ($P = 0.52$) or large for gestational age ($P = .69$).

CONCLUSION: Our findings are reassuring for women who experience weight loss or excessive weight gain in the first trimester; however, the risk of small or large for gestational age is significantly increased if women gain weight below or above the reference trajectory in the second/third trimester.

Key words: birthweight, gestational weight gain, patterns, small for gestational age, trajectory

Introduction

Gestational weight gain (GWG) has gained particular interest in public health as a potentially modifiable factor to ensure healthy pregnancy outcomes and reduce the risk of adverse outcomes.[1] The intense interest in GWG was in part prompted by gaps identified in the 2009 Institute of Medicine (IOM) report on reexamining the GWG guidelines.[1] While total GWG provides a long-term goal for pregnant women, the pattern of GWG throughout pregnancy has stronger clinical utility as a prospective monitoring tool for clinicians to identify weight gain above or below the guidelines early on, when intervention may still benefit both mother and baby. Yet, few studies in homogenous populations informed the recommended

Cite this article as: Pugh SJ, Albert PS, Kim S, et al. Patterns of gestational weight gain and birthweight outcomes in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies—Singletons: a prospective study. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00
Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ajog.2017.05.013

second-/third-trimester rates of gain[2-4] and provide little insight into the impact of first-trimester patterns in relation to birthweight outcomes. The current guidelines may obscure how varying trajectories of first-trimester weight gain impact second-/third-trimester patterns.[5] Recent evidence, aimed at addressing these data gaps, supports the notion that women may reach total GWG through various weight gain trajectories[6-8] and suggests that higher trimester-specific GWG is associated with decreased odds of small for gestational age (SGA) and increased odds of large for gestational age (LGA).[9-11] However, the majority of this evidence assessed each trimester independently, as opposed to assessing the entire trajectory of GWG throughout pregnancy. It also remains unclear whether early pregnancy GWG (eg, first trimester) sets the trajectory for subsequent second-/third-trimester GWG or if a fluctuating trajectory of GWG across trimesters differentially affects the risk of birthweight outcomes. For example, if GWG is low in the first trimester, but rapid in the second and third trimesters, does the risk of SGA differ compared with a low GWG trajectory throughout pregnancy? By characterizing the interrelationship between trajectory of GWG across trimesters, we can discover whether the trajectory of GWG in the first trimester sets the path for GWG in subsequent trimesters, serving as an early marker for at-risk pregnancies.

Our objectives were first to describe overall GWG trajectories in a contemporary, diverse, US cohort. Secondly, we aimed to calculate the risk of birthweight outcomes (SGA, LGA, SGA or LGA plus neonatal morbidity) associated with overall trajectory of GWG. Lastly, we aimed to examine the effect of an early (first trimester) vs later (second/third trimester) GWG trajectory on the risk of subsequent birthweight outcomes, to assess whether the timing of GWG was differentially associated with adverse outcomes.

Materials and Methods

We performed a secondary analysis using data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies—Singletons (n = 2802), a prospective cohort of pregnant women aged 18-40 years with a pregnancy between 8 weeks 0 days and 13 weeks 6 days (mean 12.7 [SD 0.95] weeks of gestation) from 12 US sites from July 2009 through January 2013. The primary purpose of the original NICHD fetal growth study was to establish a standard for normal fetal growth (velocity) and size for gestational age in the US population. Secondary objectives included a collection of blood samples for an etiology study of gestational diabetes and a prediction study of fetal growth restriction and/or overgrowth, and collection of dietary intake data to study the association between nutrition and fetal growth. To achieve the first objective, the study aimed to recruit 2400 healthy, nonobese (body mass index [BMI] between 19.0-29.9 kg/m^2), low-risk women across 4 race/ethnicity groups, who conceived spontaneously and had no obvious risk factors for fetal growth restriction or overgrowth, specifically, non-Hispanic White, Black, Hispanic, and Asian/Pacific Islander women (600 women in each group). In addition, the study aimed to recruit 600 obese women (BMI between 30-45 kg/m^2) with no restriction on race/ethnicity to achieve the additional study aims. Exclusion criteria were similar between nonobese and obese women and included chronic hypertension or high blood pressure under medical supervision (obese women if requiring $\geq$2 medications), pregestational diabetes, chronic renal disease under medical supervision, autoimmune disease, psychiatric disorders, cancer, and HIV/AIDS.[12] Additional exclusion criteria for the nonobese women included a history of preterm low birthweight (<2500 g), or macrosomic (>4000 g) neonate; history of stillbirth or neonatal death; medically assisted conception; cigarette smoking or illicit drug use in past 6 or 12 months, respectively; $\geq$1 daily alcoholic drinks; previous fetal congenital malformation; history of noncommunicable diseases (asthma requiring weekly medication, epilepsy or seizures requiring medication, hematologic disorders, hypertension, thyroid disease); or history of gravid diseases (gestational diabetes, severe preeclampsia/eclampsia, or hemolysis, elevated liver enzymes, low platelet count syndrome).[12] Only 1 pregnancy per mother was included in the cohort. Human subjects' approval was obtained from all participating sites and women gave informed consent.

At enrollment, research nurses conducted in-person interviews to obtain detailed demographic and health characteristics. Recalled prepregnancy weight and measured height, using a portable stadiometer (Seca Corp, Hamburg, Germany) were used to calculate prepregnancy BMI (kg/m^2). At each of the NICHD fetal growth research visits, women's weight was measured following a standardized anthropometric protocol. Maternal weight at routine antenatal clinical visits was also abstracted from the prenatal records. To improve the precision of estimates by increasing the number of measurements per women, we evaluated the quality of abstracted weights from prenatal records to see if both the measured weights as part of the study protocol and chart-abstracted weights from prenatal records could be combined. We calculated the rate of change between each weight and the next closest measurement, regardless of the source, to examine for large implausible gains/losses. A chart-abstracted and measured research visit weight occurring on the same gestational age (to the day) were within a mean of 0.04 (SD 0.95; range −10.5 to 14.5) kg (n = 2169 duplicate weights out of 45,540, 4.7%) and were highly correlated (Pearson correlation coefficient 0.998); therefore, both sources of maternal weight were used in the analysis due to their high consistency. However, to avoid redundancy, in the instances where both weights occurred on the same day, we included only the measured weights in the analysis. GWG was calculated as the difference between maternal weight and self-reported prepregnancy weight. The last maternal weight was measured at a mean of 39.2 (SD 1.66) weeks. After delivery, certified staff abstracted maternal and neonatal information from

the medical records. Birthweight at delivery was used to calculate SGA <10th and LGA ≥90th based on sex-specific birthweight references.[13] Furthermore, in an effort to identify pathologically small or large infants, babies who are small due to underlying pathologic conditions, and babies at an increased risk of morbidity and mortality,[14] we also created the following outcome measures: severe SGA (<5th percentile), SGA <10th plus neonatal morbidity, and LGA ≥90th plus neonatal morbidity. Neonatal morbidities were selected based on what was reported in the literature[15] and data availability; were defined specifically to SGA or LGA based on the likelihood of the relevant outcome; and included: metabolic acidosis (pH <7.1 and base deficit >12 mmol/L), neonatal intensive care unit stay >3 days, pneumonia, respiratory distress syndrome, persistent pulmonary hypertension, seizures, hyperbilirubinemia requiring exchange transfusion, intrapartum aspiration (meconium, amniotic fluid, blood), neonatal death, mechanical ventilation at term, necrotizing enterocolitis, hypoglycemia, hypoxic ischemic encephalopathy, periventricular leukomalacia (SGA only), sepsis based on blood culture (SGA only), bronchopulmonary dysplasia/chronic lung disease (SGA only), retinopathy of prematurity (SGA only), and birth injury (LGA only).[16-20]

Statistical analysis

To estimate the GWG trajectories, we excluded 3 women who were ineligible after enrollment and were missing prepregnancy weight and included the remaining 2779 women with at least 2 weight measurements to improve model accuracy. We used a latent-class trajectory model, a flexible semiparametric approach to discover patterns of GWG across pregnancy using *PROC TRAJ* in SAS software (SAS Institute Inc, Cary, NC).[21] This method provides a data-driven approach to identify whether there are groups of latent trajectories and the corresponding probability of falling into each group (posterior probability). We fit linear, quadratic, and cubic models to allow for model flexibility and examined model fit with 3-6 trajectories. The model with the lowest Bayesian information criterion value was selected, as this value serves to indicate model fit.[21] For descriptive analyses, women were classified into a particular trajectory group (trajectory membership) based on their highest posterior probability. The χ^2 and Fisher exact tests, where appropriate, were used to determine differences in maternal demographic characteristics by trajectory.

First, we fit the latent trajectory models to all the longitudinal data across pregnancy. To assess the tracking of weight gain, we then fit 2 separate latent trajectory models to longitudinal data collected in the first trimester (0-<14 weeks) and the second/third trimester (≥14 weeks to delivery), to inform the current first- and second-/third-trimester GWG guidelines. We classified subjects into 4 groups in each time period based on the separate latent trajectory models fit for the first and second/third trimesters. Then, we calculated the proportion of women in each trajectory combination from the first to second/third trimesters.

After the overall and trimester-specific GWG trajectories were estimated, we examined the association between the trajectories and birthweight outcomes. Among the 2779 women who were eligible for this analysis, we excluded women who had neonates with congenital anomalies (n = 107), were lost to follow-up (n = 33), refused to continue (n = 97), moved (n = 29), had stillbirth or miscarriage (n = 27), voluntarily terminated their pregnancy (n = 10), had missing covariate information (n = 3), or had missing birthweight (n = 44). The final analysis included 2429 women (Figure 1). We fit modified Poisson regression models with a robust variance estimator using the overall posterior probabilities to assess the risk of SGA and LGA, as well as SGA and LGA plus neonatal morbidity.

FIGURE 1
Analytic flow diagram for NICHD Fetal Growth Studies-Singletons

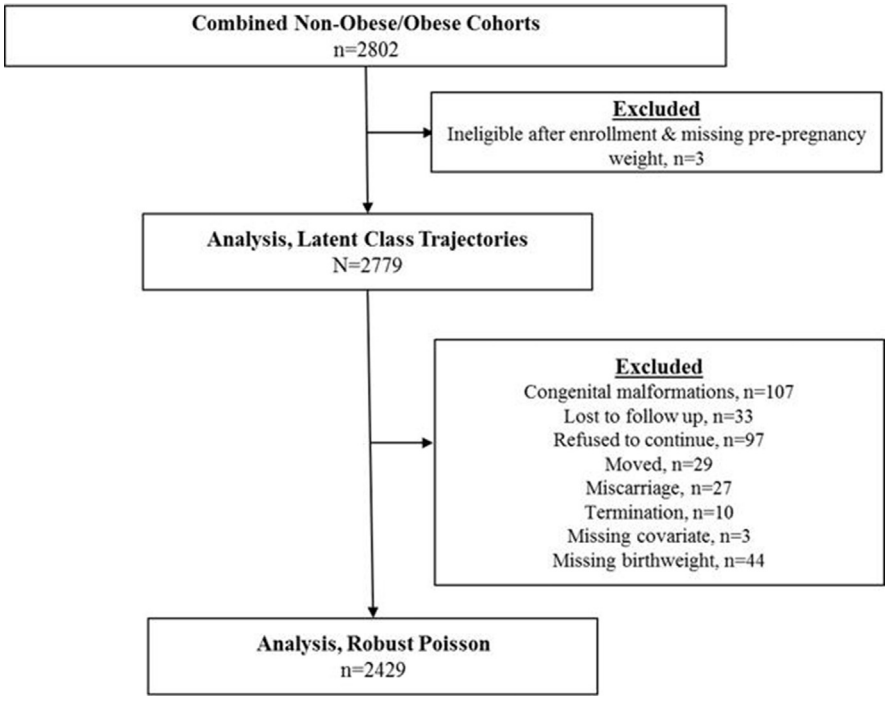

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TABLE 1
Demographic characteristics of population by trajectory membership

	Overall, n = 2779	Low GWG, n = 274	Reference GWG, n = 1173	Moderate-high GWG, n = 1099	High GWG, n = 253
	No. (%)				
Maternal age, y[a]					
<20	162 (5.7)	31 (11.3)	64 (5.4)	54 (5.0)	13 (5.3)
20–29	1463 (52.3)	165 (60.3)	623 (53.1)	535 (48.6)	140 (55.1)
30–39	1146 (41.0)	77 (28.0)	470 (40.0)	499 (45.4)	100 (39.6)
40–44	28 (1.0)	1 (0.4)	16 (1.5)	11 (1.0)	0 (0)
Insurance[a]					
Other	973 (37.7)	136 (53.0)	418 (38.9)	314 (30.8)	105 (44.2)
Private or managed	1611 (62.3)	119 (47.0)	663 (61.1)	699 (69.2)	130 (55.8)
Race/ethnicity[a]					
Non-Hispanic White	751 (26.8)	41 (14.9)	288 (24.4)	355 (32.3)	67 (26.5)
Non-Hispanic Black	781 (27.9)	113 (41.2)	297 (25.2)	286 (26.0)	85 (33.5)
Hispanic	801 (28.6)	98 (35.8)	360 (30.9)	271 (24.6)	72 (28.5)
Asian/Pacific Islander	466 (16.7)	22 (8.0)	228 (19.5)	187 (17.1)	29 (11.5)
Marital status[a]					
Never married	632 (22.5)	83 (30.3)	263 (22.4)	219 (19.8)	67 (26.5)
Married	2082 (74.5)	181 (66.1)	881 (75.0)	850 (77.3)	170 (67.2)
Divorced/widowed	83 (3.0)	10 (3.6)	27 (2.4)	30 (2.9)	16 (6.3)
Education[a]					
≤High school diploma	838 (29.9)	119 (43.1)	371 (31.5)	273 (24.9)	75 (29.7)
Some college or associates degree	850 (30.4)	102 (37.6)	326 (27.7)	319 (29.0)	103 (40.7)
Bachelors or advanced degree	1111 (39.7)	53 (19.3)	476 (40.8)	502 (46.1)	75 (29.6)
Income, $[a]					
<39,000	943 (39.0)	132 (56.4)	381 (37.9)	342 (35.3)	83 (41.5)
40,000–74,900	527 (21.8)	63 (26.9)	214 (21.3)	199 (20.5)	51 (24.6)
≥75,000	945 (39.1)	39 (16.7)	410 (40.8)	428 (44.2)	68 (33.9)
Parity[a]					
0	1316 (47.0)	105 (38.3)	536 (45.6)	543 (49.4)	132 (52.2)
1	943 (33.7)	97 (35.4)	406 (34.7)	372 (33.8)	68 (26.9)
≥2	540 (19.3)	72 (26.3)	231 (19.7)	184 (16.8)	53 (20.9)

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Models were adjusted for maternal age (<20, 20-29, 30-39, 40-44 years), prepregnancy BMI, height, parity (0, 1, ≥2), education level (≤high school diploma, some college or associates degree, bachelors or advanced degree), student status (yes/no), and race (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander). All covariates were treated as continuous unless otherwise stated (Supplemental Figure 1). We tested whether relationships were modified by prepregnancy BMI (tested both as continuous and categorical variables) or maternal race (likelihood ratio test conducted at the .05 significance level).

To examine the differential associations of early vs later GWG (corresponding to the first and second/third trimester, respectively) with the risk of subsequent birthweight outcomes, we used the separate trajectory models fit for these 2 time periods. Since the low and high GWG trajectories presented the most risk for birthweight outcomes, we were interested in assessing whether moving out of either a low or high trajectory changed the risk of birth outcomes. Therefore, we combined the

TABLE 1
Demographic characteristics of population by trajectory membership *(continued)*

	Overall, n = 2779	Low GWG, n = 274	Reference GWG, n = 1173	Moderate-high GWG, n = 1099	High GWG, n = 253
	No. (%)				
Prepregnancy BMI, kg/m^2[a]					
Normal weight, 18.5–24.9	1575 (56.3)	78 (28.5)	695 (59.3)	684 (62.4)	117 (46.6)
Overweight, 25–29.9	750 (26.8)	81 (29.6)	289 (24.7)	285 (25.9)	95 (37.3)
Obese, >30.0	474 (16.9)	115 (41.9)	188 (16.0)	130 (11.7)	41 (16.2)
Preterm birth[a]					
<37 wk	2290 (94.3)	21 (8.80)	56 (5.50)	45 (4.70)	17 (7.80)
≥37 wk	139 (5.70)	21 (91.2)	968 (94.5)	905 (95.3)	200 (92.2)

GWG trajectories identified from latent class trajectory models and women grouped based on highest probability of group membership; median posterior probability 0.99 (interquartile range 0.99–1.0) for all groups.

BMI, body mass index; *GWG*, gestational weight gain.

[a] χ^2 Test or Fishers exact test *P* value < .05 for differences in demographic characteristics across GWG trajectory groups.

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remaining categories, since it was rare that an individual switched between low and high groups (n = 1 from low to high GWG; n = 0 from high to low GWG).

The low and high GWG groups presented the most risk for birthweight outcomes; therefore, we characterized the effects of changing from each of these groups between the first and second/third trimester using the following 2 classification schemes. First, to examine differential effects from the lowest GWG group, we classified subjects as being in 1 of the following 4 groups for the first to second/third trimesters: referent to referent; low to low; low to referent or moderate-high or high; and referent or moderate-high or high to low. Second, to examine differential effects from the highest GWG group we classified subjects as being in 1 of the following 4 groups for the first to second/third trimesters: referent to referent; high to high; high to low or referent or moderate-high; and low or referent or moderate-high to high.

Additionally, to assess the potential bias by pregnancy/birth complications or differences between nonobese and obese women, we conducted a sensitivity analysis to explore GWG trajectories in a subset of the cohort, the NICHD fetal growth studies standard[12] (n = 1731), restricted to a group of nonobese, low-risk women without specific pregnancy complications such as preterm birth, gestational diabetes, or preeclampsia, or infants with neonatal conditions such as anomalies, aneuploidy, or death. Analyses were conducted using software: SAS, Version 9.4 (SAS Institute Inc) and Stata, Version 13.0 (StataCorp, College Station, TX).

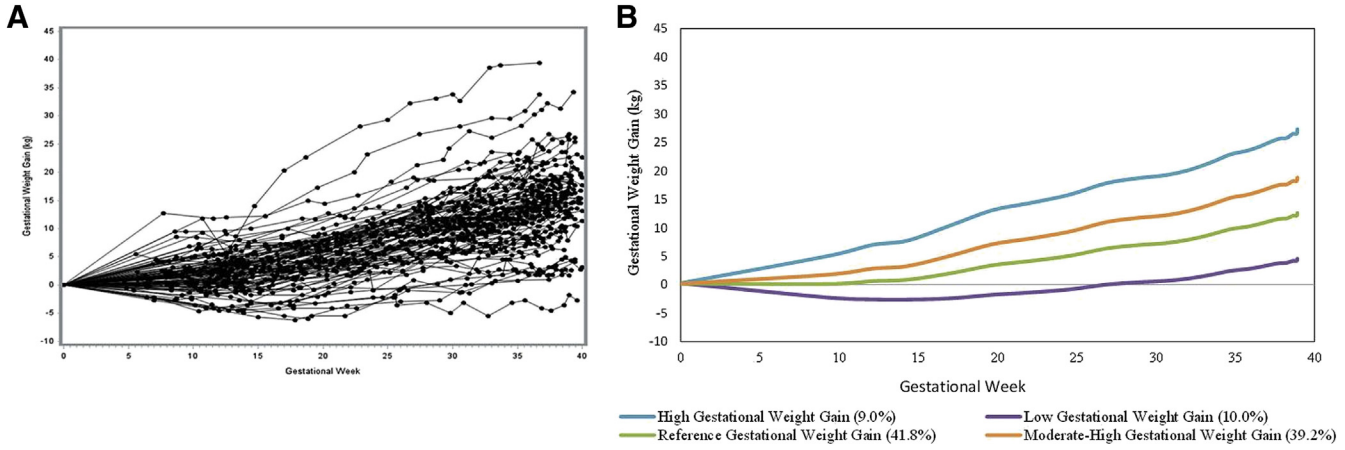
Results

In the 2779 women in the cohort, the majority were 20-39 years of age (93%), married (74.9%), and of normal weight (56.2%) (Table 1). The racial composition was evenly distributed as per study design between non-Hispanic White, non-Hispanic Black, and Hispanic women, although there was a smaller proportion of Asian women (16.1%). The mean number of measured weights per woman was 15 (SD 5), which was composed of both the measured (mean 4.2 [SD 0.99]) and abstracted (mean 11.3 [SD 2.8]) weights.

Figure 2 depicts the raw GWG trajectories from a random sample of 100 women (Figure 2, A) in comparison with the modeled latent trajectory data (Figure 2, B) to illustrate the accurate fit of the latent models. The latent class trajectory approach identified a cubic model with 4 distinct weight gain trajectory groups, classifying 10.0%, 41.8%, 39.2%, and 9.0% of the population from lowest to highest weight gain trajectories, with an inflection point at 14 weeks' gestation (Figure 2). The average rate in each trajectory group from lowest to highest for 0-<14 weeks was −0.20, 0.04, 0.21, and 0.52 kg/wk and for 14-39 weeks was 0.29, 0.48, 0.63, and 0.79 kg/wk (Table 2). The second lowest gaining trajectory most closely resembled the IOM GWG recommendations for normal-weight women[1] and was therefore designated as the reference GWG group, with the other trajectories classified as low, moderate-high, or high. In the analysis limited to the NICHD Fetal Growth Studies—Singletons standard,[12] composed of 1737 nonobese women at low risk for fetal growth abnormalities, the latent class trajectory approach identified only 2 trajectories that approximated the reference and moderate-high trajectories (Supplemental Figure 2).

The latent class trajectory models also assessed the accuracy of assignment (ie, the posterior probability) of each individual woman to 1 of the 4 groups. For all individuals, the median posterior probability of assignment to a given class was 0.99 (interquartile range 0.99-1.0),

FIGURE 2
Raw and modeled gestational weight gain trajectories



A, Random sample of 100 raw gestational weight gain (GWG) trajectories. **B**, Identified GWG trajectories from latent class model; separate colors indicate different GWG classes.

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indicating confidence in the classification.

Demographic characteristics differed by overall GWG groups (Table 1). Compared with the reference and moderate-high GWG groups, women in the low GWG group were less likely to have private or managed insurance and income ≥$75,000, and more likely to have less education and be non-Hispanic Black (Table 1). The prevalence of SGA <10th percentile decreased with increasing overall GWG trajectory group from 15.3% in the low GWG group to 5.2% in the high GWG group. In contrast, the percent of LGA ≥90th percentile increased with increasing GWG class from 3.7-16.9% for the low GWG to high GWG group (Table 3).

Compared with a reference GWG trajectory across the entire pregnancy, low GWG was associated with a 55% increased risk of SGA <10th percentile (relative risk [RR], 1.55; 95% confidence interval [CI], 1.06−2.25) and a 62% decreased risk of LGA (RR, 0.38; 95% CI, 0.17−0.85). A similar trend was observed for SGA <5th percentile and SGA plus neonatal morbidity, although none of the estimates were significant. A high GWG trajectory was associated with a 2.5-fold increased risk of LGA (Table 4). The sample size was too small to accurately estimate the risk of LGA plus neonatal morbidity. The low GWG trajectory was composed of 42% of obese women, although that only accounted for 24.3% (n = 115) of obese women in the study; obese women comprised 39.7% of the reference, 27.4% of the moderate-high, and 8.6% of the high GWG trajectories. When we evaluated whether prepregnancy BMI modified the association between GWG trajectory and risk of adverse birthweight outcomes, there was no effect: SGA <10th percentile ($P = .52$), SGA <5th percentile ($P = .61$), SGA plus neonatal morbidity ($P = .60$), or LGA ≥90th percentile ($P = .69$); therefore, we did not stratify our results by prepregnancy BMI. Similarly, since relations did not vary by race/ethnicity, we did not stratify our results.

Table 5 depicts GWG tracking from the first to second/third trimesters. Among women with low GWG in the first trimester, 49.6% continued to have low GWG in the second/third trimesters, while 45% and 5.4% increased

TABLE 2
Trimester-specific rate of gestational weight gain corresponding to entire pregnancy trajectories in Figure 2

	First trimester, 0−<14 wk Mean (95% CI)	Second + third trimester, >14 wk to delivery Mean (95% CI)
	Rate of gain, kg/wk	Rate of gain, kg/wk
Low GWG	−0.20 (−0.19 to −0.21)	0.29 (0.28−0.30)
Reference GWG	0.04 (0.04−0.05)	0.48 (0.47−0.48)
Moderate-high GWG	0.21 (0.21−0.22)	0.63 (0.63−0.64)
High GWG	0.52 (0.51−0.53)	0.79 (0.79−0.80)

CI, confidence interval; *GWG*, gestational weight gain.

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TABLE 3
Prevalence of birthweight outcomes by gestational weight gain trajectory group

	Low GWG, n = 274	Reference GWG, n = 1173	Moderate-high GWG, n = 1099	High GWG, n = 253
	No. (%)			
SGA				
SGA <10th percentile[a]	37 (15.3)	103 (10.3)	69 (7.9)	10 (5.2)
SGA <5th percentile[a]	17 (6.9)	51 (4.9)	29 (3.1)	6 (2.9)
SGA<10th percentile plus neonatal morbidity	3 (1.5)	6 (0.7)	2 (0.3)	2 (1.2)
LGA				
LGA ≥90th percentile[a]	8 (3.7)	67 (6.9)	114 (12.3)	37 (16.9)
LGA≥90th percentile plus neonatal morbidity	0 (0)	3 (0.35)	7 (0.90)	2 (1.2)

GWG, gestational weight gain; *LGA*, large for gestational age; *SGA*, small for gestational age.

[a] χ^2 Test or Fishers exact test *P* value <.001 for group differences.

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their GWG trajectory to the reference GWG or moderate-high GWG, respectively. Among the 52 women with high GWG in the first trimester, a high proportion (75%) continued to have high GWG until delivery. Among women with reference GWG in the first trimester, most gained in the reference (46%) or moderate-high (44%) in the second/third trimesters, while approximately one third (35%) of women with moderate-high weight gain in the first trimester had high GWG in the second/third trimesters.

The risk of SGA differed based on the first- to second-/third-trimester pattern of GWG. Women with low GWG in both the first and second/third trimesters had a 1.59-fold (95% CI, 1.04−2.52) increased risk of SGA <10th percentile, compared with reference GWG in both periods. In contrast, women with a low GWG trajectory in the first trimester but referent, moderate-high, or high GWG trajectory in the second/third trimester had no increased risk of SGA. Women with low GWG only in the second/third trimesters but not in the first had a 1.52-fold (95% CI, 0.87−2.66) increased risk of SGA (Figure 3). For the risk of LGA, women with high GWG in both the first and second/third trimesters had a 2.33-fold (95% CI, 1.11−4.87) increased risk of LGA, and women with a low, referent, or moderate-high trajectory in the first trimester, but high in the second/third trimesters had a 2.46 (95% CI, 1.66−3.65) increased risk of LGA. There were too few women with high GWG in the first trimester to obtain all estimates.

Comment

In a modern, diverse cohort of pregnant women, 4 trajectories of overall GWG were evident. The GWG trajectory with a mean of 0.04 kg/wk <14 weeks of gestation and 0.48 kg/wk from 14-39 weeks of gestation was associated with the lowest risk of SGA or LGA. Women following a low GWG trajectory across the entirety of pregnancy had an increased risk of SGA while women with a high trajectory had an increased risk of LGA, suggesting the importance of the reference trajectory in balancing the risk of either outcome. The association between GWG and SGA and LGA was no longer evident when a low or high first-trimester trajectory did not continue on the same low or high trajectory for the second/third trimesters. These findings highlight that the risk of SGA was

TABLE 4
Risk of birthweight outcomes by gestational weight gain trajectory

	Percent in each group	SGA <10th percentile plus neonatal morbidity[a] RR (95% CI)	SGA <5th percentile[a] RR (95% CI)	SGA <10th percentile[a] RR (95% CI)	LGA ≥90th percentile[a] RR (95% CI)
Overall					
Low GWG	10.0	1.56 (0.28−8.69)	1.58 (0.88−2.82)	1.55 (1.06−2.25)	0.38 (0.17−0.85)
Reference GWG	41.8	Reference	Reference	Reference	Reference
Moderate-high GWG	39.2	0.51 (0.12−2.10)	0.57 (0.35−0.94)	0.75 (0.55−1.02)	1.78 (1.31−2.41)
High GWG	9.0	1.14 (0.19−6.82)	0.50 (0.19−1.27)	0.51 (0.25−1.00)	2.45 (1.66−3.61)

Corresponds to latent trajectory posterior probabilities.

CI, confidence interval; *GWG*, gestational weight gain; *LGA*, large for gestational age; *RR*, relative risk; *SGA*, small for gestational age.

[a] Model 1: adjusted for insurance, race, student status, education, parity, height, prepregnancy body mass index, age.

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TABLE 5
Proportion of women in each gestational weight gain trajectory from first-trimester gestational weight gain to second/third trimesters

	Second-/third-trimester trajectory[a]			
First-trimester trajectory[a]	Low GWG	Reference GWG	Moderate-high GWG	High GWG
Low GWG	127/256 (49.6%)	114/256 (44.5%)	14/256 (5.5%)	1/256 (0.4%)
Reference GWG	83/1696 (5%)	781/1696 (46%)	737/1696 (44%)	95/1696 (5%)
Moderate-high GWG	4/436 (0.9%)	45/436 (10.5%)	238/436 (54.3%)	149/436 (34.3%)
High GWG	0/53 (0%)	2/53 (3.8%)	11/53 (21.2%)	39/53 (75%)

GWG, gestational weight gain.

[a] Women were each assigned trajectory when their individual probability was >0.80 for particular trajectory based on latent class models. Women without individual trajectory probability of >0.80 were classified to trajectory with highest posterior probability (n = 215 reclassified first trimester and n = 108 reclassified second/third trimester).

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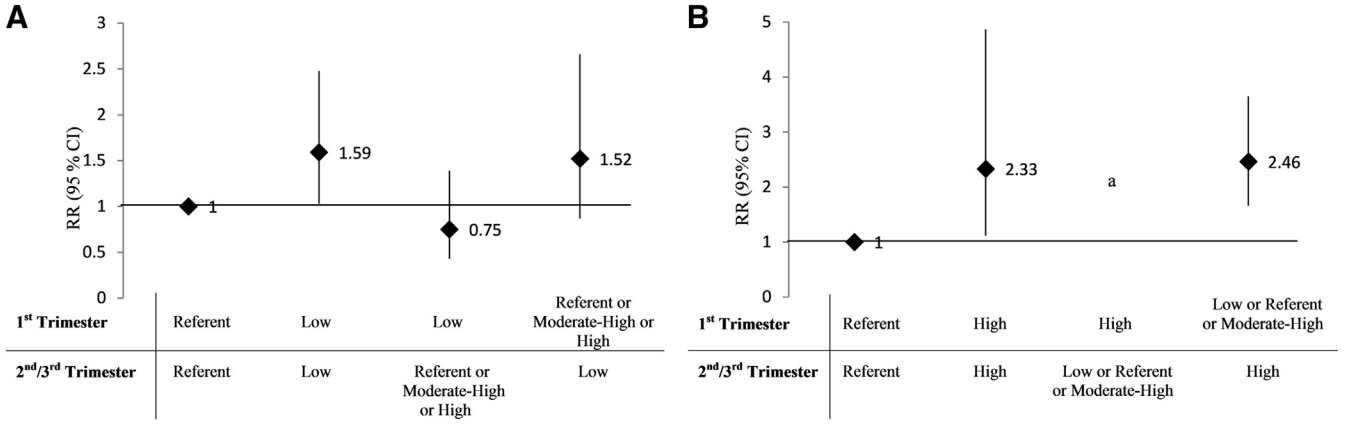
only increased based on second-/third-trimester GWG. When only the second-/third-trimester GWG trajectory was low, the risk of SGA was similar to when both the first- and second-/third-trimester trajectories were low and when only second-/third-trimester GWG was high, the risk of LGA was similar to when both the first- and second-/third-trimester trajectories were high. Both of these findings underscore the importance of maternal GWG in the second and third trimesters.

The main new contribution of our study is the assessment of the interrelationship between the first- and second-/third-trimester trajectories on these risks. In a previous cluster analysis using a small, homogenous cohort of 325 healthy pregnant women from Belgium, 4 weight gain trajectories were identified and a dose-response relationship was reported between the overall GWG trajectory and birthweight at delivery.[6] Compared with the trajectories identified by Galjaard et al[6] in 2013, our trajectories were shifted upward toward higher GWG, a difference that may be related to fact that the low GWG classification was established by Galjaard et al[6] in 2013 based on only a few cases in the context of a small sample size. Our finding relating GWG trajectories to birthweight outcomes was also similar to a study of 651 overweight and obese women from Pittsburgh, which identified 4 GWG trajectories and reported that a consistently high GWG trajectory was

FIGURE 3
Risk of small for gestational age and large for gestational age based on first to second/third trimester gestational weight gain



Risk of **A**, small and **B**, large for gestational age by combined trajectory of gestational weight gain from first to second/third trimesters. Women were each assigned trajectory when their individual probability was >0.80 for particular trajectory based on latent class models. Women without individual trajectory probability of >0.80 were classified to trajectory with highest posterior probability (n = 215 reclassified first trimester and n = 108 reclassified second/third trimester). [a]Missing estimates due to small numbers.

CI, confidence interval; *RR*, relative risk.

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associated with a 4.6-fold increased odds of LGA while a consistently low GWG trajectory was associated with a 1.2-fold increased odds of SGA, compared with women with adequate weight gains.[8] The existing literature assessing the timing of GWG is small and has suggested that increasing first-trimester[9-11] as well as second- and third-trimester[9] GWG is associated with a decreased odds of SGA, but an increased odds of LGA. Importantly, in our analysis, we observed an association between first-trimester GWG and birthweight outcomes only when low or high GWG tracked into the second/third trimesters. In addition, our findings build on this literature by utilizing a longitudinal approach to inform how the entire trajectory of GWG indicates risk for birthweight outcomes, as opposed to assessing trimester-specific gains as independent time periods.

Clinical guidance regarding caloric intake is an important factor linked to actual maternal weight gain.[22] Prospective monitoring could improve early identification of a poor (low or high) weight gain trajectory and then serve as a prompt for clinicians to refer high-risk women to registered dietitians to counsel on lifestyle to potentially help reach optimal weight gain and with the goal of improving obstetric outcomes. Unfortunately, evidence suggests that clinicians infrequently provide any or accurate weight gain advice.[22,23] While the IOM recommended lower total GWG for overweight and obese women, we found that prepregnancy BMI did not modify the association between GWG trajectory and birthweight outcomes. Furthermore, after excluding complicated pregnancies, the reference trajectory remained unchanged and was not associated with adverse birthweight outcomes, which could support the reference trajectory as an optimal pattern for maternal and infant outcomes. Future research should address the causal link between modifying weight gain and improved birthweight outcomes and expand our findings to include long-term maternal and child health outcomes.

Given that our study is observational, we cannot determine a causal link between a modified GWG trajectory from the first to second/third trimesters and a reduced risk of aberrant birthweight outcomes. Due to a small sample size, we were unable to estimate the risk of LGA by some high GWG tracking combinations and stratified analyses. The identified trajectories were limited by the reliance on self-reported prepregnancy weight, the accuracy of which may vary by maternal characteristics, although evidence suggests BMI remains accurately classified in 85% of pregnancies[24] and recalled prepregnancy weight is often used in clinical practice, enhancing the utility of our findings. Furthermore, the birthweight reference used to calculate SGA and LGA was composed of mostly White women and applied to a racially diverse cohort. Another limitation of this study is the lack of long-term outcomes such as postpartum weight retention, child cognitive development, and metabolic profiles to assess the long-term health implications of GWG patterns. The inclusion criteria for the NICHD fetal growth studies were limited by design to healthy women with a lower-limit BMI of 19.0; therefore, we cannot make inferences about underweight women or women with general health complications. Limitations of our study reflect the observational design, including potential bias from the inclusion/exclusion criteria used for cohort selection. As our aim was to assess GWG trajectories in a low-risk healthy cohort, our findings might not be generalizable to higher-risk obstetrical populations. Also, our study only assessed GWG, but not caloric intake or nutrition directly. Yet, the major advantage of our study was the inclusion of a racially and geographically diverse cohort of healthy women enabling us to identify patterns of weight gain unaffected by health conditions prior to pregnancy. This study was also strengthened by its longitudinal design with an average of 15 weight measurements per women, which increased the precision of estimated GWG trajectories. The use of a latent trajectory model allowed for a data-driven approach to identify clusters of weight gain. In addition, the inclusion of SGA plus neonatal morbidity and SGA <5th percentile provides insight into the potential risk of pathologically small infants associated with low or high GWG trajectories, although this finding is limited by a small sample size. Lastly, our study extends the current literature by highlighting the prevalence and implications of GWG tracking from the first to second/third trimesters.

In conclusion, our findings are reassuring for women who experience weight loss or excessive weight gain in the first trimester. Achieving a reference trajectory in the second/third trimester will normalize their risk of SGA and LGA. However, the risk of SGA and LGA is significantly increased if they gain weight below or above the reference trajectory in the second/third trimester. Early clinical recognition of a poor GWG trajectory may help to detect at-risk pregnancies and serve as a prompt to discuss optimal weight gain, but ultimately, low or high second-/third-trimester GWG presents a significant added risk for adverse birthweight outcomes. ■

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Received Jan. 25, 2017; revised April 28, 2017; accepted May 4, 2017.

This project was supported by the intramural program at *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and included American Recovery and Reinvestment Act funding (contract numbers: HHSN 275200800013C; HHSN275200800002I; HHSN275000 06; HHSN275200800003IC; HHSN275200800014C; HHSN275200800012C; HHSN275200800028C; HHSN 275201000009C).

The authors report no conflict of interest.

Preliminary results were presented during the Society for Pediatric and Perinatal Epidemiology conference, Miami, FL, June 19-20, 2016.

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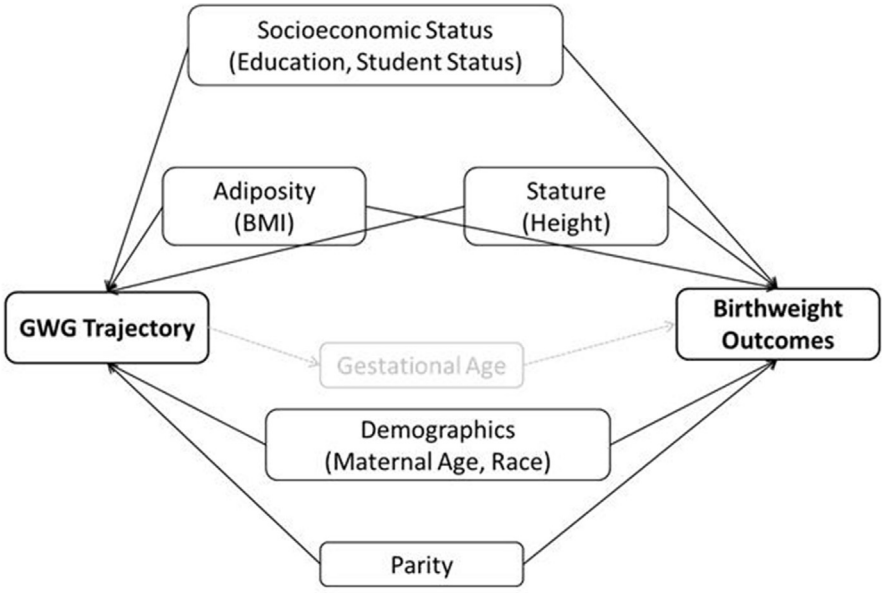
SUPPLEMENTAL FIGURE 1
Directed acyclic graph



Directed acyclic graph representing relationship between gestational weight gain (GWG) trajectories and birthweight outcomes and associated confounders. Factors on causal pathway not included in adjustments (light gray boxes).

BMI, body mass index.

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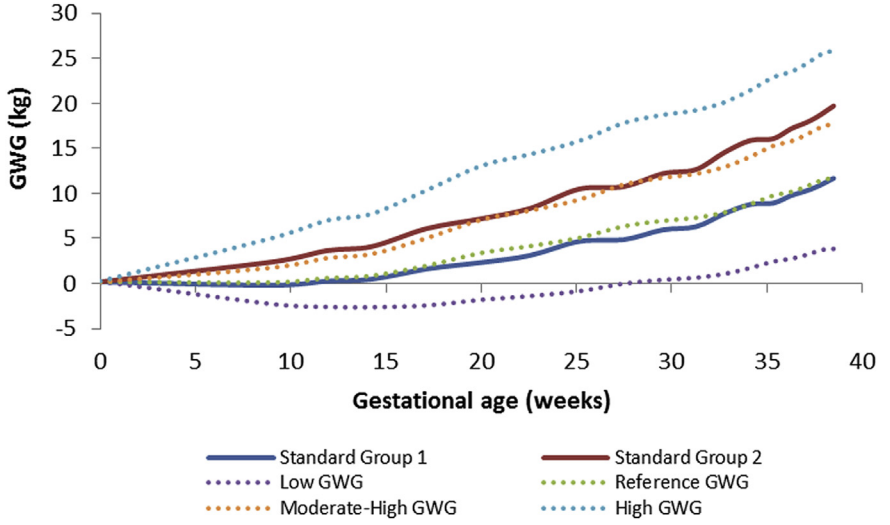
SUPPLEMENTAL FIGURE 2
Standard population GWG trajectories



Sensitivity analysis modeling *Eunice Kennedy Shriver* National Institute of Child Health and Human Development fetal growth studies standard population (bold lines) overlaid on main analysis (dotted lines).

GWG, gestational weight gain.

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