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Prenatal weight and regional body composition trajectories and neonatal body composition: the NICHD Fetal Growth Studies

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Abstract

Background: Gestational weight gain (GWG) and anthropometric trajectories may affect fetal programming, and are potentially modifiable.

Objectives: To assess concomitant patterns of change in weight, circumferences and adiposity across gestation as an integrated prenatal exposure, and determine how they relate to neonatal body composition.

Methods: Data are from a prospective cohort of singleton pregnancies (n=2,182) enrolled from United States perinatal centers, 2009–2013. Overall and by prepregnancy BMI group (overweight/obesity and healthy weight), joint latent trajectory models were fit with prenatal weight, mid-upper arm circumference (MUAC), triceps (TSF) and subscapular (SSF) skinfolds. Differences in neonatal body composition by trajectory class were assessed via weighted least squares.

Results: Six trajectory patterns reflecting co-occurring changes in weight and MUAC, SSF and TSF across pregnancy were identified overall, and by BMI group. Among people with a healthy weight BMI, some differences were observed for neonatal subcutaneous adipose tissue, and among individuals with overweight/obesity some differences in neonatal lean mass were found.

Neonatal adiposity measures were higher among infants born to individuals with prepregnancy overweight/obesity.

Conclusions: Six integrated trajectory patterns of prenatal weight, subcutaneous adipose tissue and circumferences were observed that were minimally associated with neonatal body composition, suggesting a stronger influence of prepregnancy BMI.

Keywords

Gestational weight gain; body composition; pregnancy; infancy; adiposity; trajectory modeling; latent class analysis

Introduction

Gestational weight gain (GWG) above the 2009 Institute of Medicine (IOM, now the National Academies of Science, Engineering and Medicine) guidelines is associated with an increased risk of adverse outcomes for both pregnant people and their children.^{1, 2} A majority of pregnant people in the United States (US) gain in excess of the IOM guidelines.³ Interventions designed to support healthy GWG have been only moderately successful at reducing total GWG to recommended levels.^{4, 5} This may be because of the need for more intensive interventions to help pregnant people limit daily energy intakes—especially individuals with obesity, who can meet the guidelines without an increase in energy intake.^{6–8} More personalized guidance to support pregnant people in optimizing their GWG is needed. Attention to the trajectory patterns of GWG, adipose tissue accretion and other regional anthropometric changes might be one way to provide such insight and guidance. Regional skinfold thickness—reflecting subcutaneous adipose tissue and circumference changes in particular, may reflect the location of adipose tissue depot changes—either mobilization or deposition—across gestation with shifts in the iliac crest and subscapular region reflecting the more metabolically active abdominal/trunk region, whereas changes in the mid-thigh and arm regions reflecting shifts in the limb region. Shifts in GWG and its composition reflect both the uterine milieu and the nutrient stores available to support fetal growth and development, and may offer insight about developmental programming of offspring adiposity, and are feasible to measure in clinical practice; yet, very few studies have examined how the composition and patterns of these weight changes impact neonatal adiposity.^{9–14}

Neonatal fat mass is predominately subcutaneous, rather than intraabdominal or visceral,¹⁵ and is a more sensitive measure of adiposity than weight or length-derived indices. Prenatal determinants of neonatal and child adiposity, including GWG (total, pattern, and composition) and the prenatal metabolic milieu, are of growing interest in the research and clinical community.¹⁶ Previous research has demonstrated that GWG above the IOM recommendations is associated with greater neonatal adiposity, particularly among people with prepregnancy overweight¹⁷ or healthy BMI category,¹⁸ and further that effects of high GWG have long term effects on child adiposity.^{19, 20} Although prior studies have evaluated associations between GWG patterns and neonatal birthweight, very few have reported associations between GWG patterns and/or prenatal adipose tissue changes with neonatal adiposity. In a Colorado-based birth cohort, high rates of GWG in early, mid, and

late gestation were positively associated with neonatal adiposity.¹² In a subset of participants with prepregnancy healthy weight or overweight in the NICHD Fetal Growth Study (FGS)—Singletons, weight change rates in the second and third trimesters were positively associated with neonatal size and body composition.¹³ Even modeled over time, however, GWG is still a summary measure, and may have different biological effects depending on where the adipose tissue is stored and mobilized across gestation. No prior study has considered the nuanced and dynamic features of concomitant weight, circumference and regional adipose tissue accrual across pregnancy, and further, whether these changes relate to neonatal adiposity.

To support the mechanistic understanding of the developmental origins of obesity, and the development of evidence-based guidelines and interventions supporting prenatal health, a more dynamic understanding of anthropometric changes, adipose tissue accrual, and how they co-occur across pregnancy is needed. Therefore, we jointly examined concomitant changes in pregnant people's weight, subcutaneous adipose tissue, and circumferences across gestation, and then evaluated how these change patterns as an integrated prenatal exposure relate to neonatal body composition among the sizable and diverse cohort of pregnant people followed prospectively in the NICHD-FGS-Singletons. We hypothesized that patterns of change typified by higher GWG in early and mid-pregnancy coupled with greater gains in skinfolds and circumferences would be associated with greater neonatal size and adiposity.

Methods

This a secondary analysis of data from the NICHD FGS—Singletons, which was designed to develop a national normative standard for fetal growth in the US and has been previously described.^{21, 22} Briefly, from July 2009 to January 2013, pregnant people who self-identified as non-Hispanic White, non-Hispanic Black, Hispanic, and Asian or Pacific Islander were enrolled at 12 US clinical sites. Enrollment criteria included singleton pregnancy at 8–13 weeks gestation at study entry, age 18–40 years, non-smoking, body mass index (BMI) 19.0–29.9 (non-obese group) or BMI 30.0–45.0 kg/m² (obese group), and no major chronic disease. Among the non-obese group, additional exclusion criteria included: history of gestational diabetes (GDM), stillbirth, neonatal death, preterm delivery <34 weeks, and offspring birthweight <2.5 kg or >4.5 kg. Written informed consent was obtained from all participants.

Prenatal visits included a screening visit with ultrasound to confirm gestational dating, and up to five follow-up visits at regularly staggered intervals between 16–41 weeks. Trained research staff conducted anthropometric measurements using a standardized protocol (training and protocol details are in the Online Supplemental Material Extended Methods).²³ Prenatal study visit measurements (Mean: 5.3) included: weight (beam balance or digital scale), height (Seca 214, Shorr Board or wall-mounted approved stadiometer), mid-upper arm circumference (MUAC) with a non-stretchable tape measure, and triceps (TSF) and subscapular (SSF) skinfold thickness with Lange calipers. Both study visit and clinical record abstracted prenatal weights (Mean 18.1±3.2 per participant) were used in analyses. Neonatal measures were conducted within 12 to 24 hours after birth²³ and included: length

with a recumbent length board (Seca 416); weight with infant-beam balance or digital scale; MUAC with a non-stretchable tape measure; and triceps, subscapular, anterior thigh, and abdominal flank skinfold thicknesses with Lange calipers. Birthweight and gestational age at delivery were abstracted from delivery records.

Prepregnancy BMI was calculated from self-reported prepregnancy weight, which was highly correlated with measured weight at the first study visit (correlation coefficient $r=0.97$, $p<0.001$), and measured height. Birthweight and gestational age at delivery were used to categorize infants as large for gestational age (LGA, $\geq 90\%$ percentile) and small for gestational age (SGA, $<10\%$ percentile) using newborn sex-specific references.²⁴ Sex-specific neonatal BMIZ (BMI z-scores) from the World Health Organization (WHO) were also calculated, as these predict obesity risk better than weight-for-length.^{25, 26} The sum of neonatal skinfolds was calculated by adding the values for abdominal flank, anterior thigh, triceps, and subscapular values. Neonatal fat mass was estimated using a prediction equation (Catalano) with birthweight, birth length, and abdominal flank skinfold thickness.²⁷ Neonatal lean mass was calculated as birthweight minus fat mass, and percentage body fat was calculated as fat mass over birthweight times 100.

Statistical methods

Statistical analyses were conducted in R and are more extensively described in the Online Supplemental Material Extended Methods. To be included in this analysis, participants needed at least 4 prenatal weight measures and delivery on or after 37 weeks. All analyses were conducted in steps for the overall sample, and then also stratified by prepregnancy BMI into (1) healthy weight BMI category and (2) overweight/obesity BMI categories; further stratification into overweight or obesity categories was not possible due to small cell sizes for some parity and race covariates in the trajectory class groups, which would limit adjustment in our analyses. *Step 1:* fitting joint latent class model with prenatal weight and anthropometric measures and determining best model fit, *Step 2:* using the latent classes identified in step one to compare participant characteristics between the classes, *Step 3:* using the latent classes to compare neonatal outcomes by the latent classes pattern and, *Step 4:* sensitivity analyses.

First, GWG and regional anthropometric (MUAC, SSF, and TSF) change trajectories across gestation were jointly modeled using a latent class model (LCM) using an expectation-maximization (EM) algorithm that included prepregnancy BMI as a continuous variable in the class membership component of the model specification, analogous to BMI adjustment (Figure 1).²⁸ Within each latent class, changes in parameters over time were modeled for (1) weight changes as a function of gestational age with low-rank thin-plate splines with five knots at 0, 10, 20, 30, and 40 gestational weeks, class-specific error variances, and individual-specific random slopes, and (2) regional body composition (MUAC, SSF, and TSF) values (up to six per participant) with quadratic polynomials for gestational age and individual random intercepts. To select the model for use in subsequent analyses, we fit models with four, five, and six latent classes and used Bayesian Information Criterion (BIC) and the proportion of participants in each class (5% per group) to guide the choice of the number of latent classes for use in subsequent steps. The six-class model was selected

because it had the lowest BIC of the three models overall and by BMI category. Latent class membership was estimated using the posterior probability of class membership and participants were assigned to the class with the highest probability. Second, descriptive statistics for each class were estimated overall and by BMI category. Third, we estimated pairwise differences and bootstrap confidence intervals for each neonatal outcome by the pattern groups. For our sensitivity analyses, we examined whether assigning participants to with partial assignments (i.e., partial assignment to multiple latent classes) rather than to the highest probability, changed observed associations between the trajectories and neonatal outcome measures. Additionally, as GWG patterns before and after GDM diagnosis may be different, we also refit the joint model excluding GDM cases (n=114) to examine whether inclusion of GDM cases impacted model fit and the GWG curves.

Results

Of the 2,762 participants in the FGS—Singletons, GWG trajectories were estimated for 2182 pregnant people, while neonatal size data were available for up to 2027 neonates depending on the specific measurement (Figure 2). Pregnant people's baseline characteristics between those included versus excluded from the analytic sample are shown in Supplemental Table 1. A larger portion of those included in the analysis had greater than high school education, income greater than \$50,000, were married, and were Non-Hispanic white, Asian, and Hispanic, while fewer were Non-Hispanic Black. Overall, a majority of those in the analytic sample were married, and over half had a prior pregnancy and gained above the IOM GWG guidelines, while mean infant BMIZ scores were lower than the WHO reference (Table 1 & Table 2).

Gestational weight gain, regional body composition and anthropometric trajectory models

The best-fitting joint model identified six trajectory pattern groups of GWG, subcutaneous adipose tissue and MUAC, both among the overall cohort and within each of the stratified by prepregnancy BMI groups (Figure 3). These co-occurring patterns of change in weight, MUAC, TSF and SSF across gestation show the composition of weight shifting across gestation in different body regions. For example, those with prepregnancy healthy weight in **Class 6** (pink, Figure 3) showed very high initial weight gain in early pregnancy and then high weight gain subsequently across gestation (top row of Figure), and these changes were also seen in the higher starting values and earlier pregnancy increases of MUAC, SSF and TSF that attenuated with increasing gestational age (rows 2–4 of Figure 3). By contrast, in those who showed weight loss initially during pregnancy and then more rapid weight gain after 20 weeks gestation (**Class 5**, blue), MUAC was flat initially from 10–20 weeks, while SSF and TSF both increased more rapidly initially and then subsequently had a smaller increase as pregnancy progressed.

As shown in Figure 3, overall (Panel A) and when stratified by BMI category (Panel B & C), two estimated GWG patterns showed higher initial weight gains in early pregnancy [**Class 6** and **Class 2**], while two patterns had lower first trimester gains [**Class 3** and **Class 4**]. One pattern showed more weight stability in the first trimester [**Class 1**] and one pattern showed weight loss in early pregnancy [**Class 5**]. To further contextualize the

GWG patterns shown in Figure 3, Table 2 (overall sample) and Supplemental Table 2 (stratified by BMI category) provides estimated weight gain rates by trimester as well as other characteristics for each trajectory class group. Overall, all six patterns showed weight gain in the second and third trimesters, with differing weight change velocities (Table 2): the highest velocity was observed in the **Class 5** group in the second and third trimesters, whereas the lowest velocity was seen in the **Class 4** group in the second trimester, and the **Class 2** group in the third trimester. When stratified into healthy and overweight/obesity categories, generally similar rate patterns are observed with lower rates among those with prepregnancy overweight/obesity, compared to those with prepregnancy healthy BMI values (Supplemental Table 2).

Among the overall sample and by BMI category, Supplemental Table 3 shows MUAC, TSF and SSF estimates from the model by trajectory class group. Initial regional body composition (MUAC, SSF, TSF) estimates measured in early pregnancy (~10 weeks gestation) and changes across pregnancy generally followed similar patterns to one another by the trajectory group membership from the joint model overall (Figure 3 - Panels D, G, J). Overall, the highest estimated MUAC, SSF, TSF trajectories were generally among those in **Class 6**, and the lowest were among those in **Class 1**. For the groups with lower initial estimates for regional measures (**Class 1, Class 5, Class 3**), each group showed some increases in values over time with varying slopes, whereas, for the groups with higher initial estimates (**Class 2, Class 4, Class 6**), regional estimates were relatively stable or even decreased over time. GWG patterns were generally similar between the BMI categories (Healthy weight vs. Overweight and obesity) (Figure 3: Panels B & C), while MUAC, SSF and TSF showed more heterogenous initial values and changes over time in measures when stratified by BMI (Figure 3).

For the overall sample (Table 1), several prenatal characteristics were similar across the trajectory class groups, including height, and gestational age at delivery, while age, education, parity, GDM prevalence, and racial/ethnic group showed some differences by trajectory class membership. When stratified by BMI category (Supplemental Tables 4 & 5), similar differences were observed by trajectory class membership.

Neonatal size characteristics by gestational weight gain and body composition trajectory group:

Overall, unadjusted mean neonatal BMIZ were all below 0, with the lowest values among infants of mothers in **Class 1** and **Class 4** and the highest among infants of mothers in **Class 3 & 5** (Table 1). Overall percentage body fat in the neonates was 12.4% with the lowest values among **Class 1** and highest among **Class 4**. When stratified into healthy and overweight/obesity prepregnancy BMI categories, mean neonatal BMIZ scores were lower among infants exposed to prepregnancy healthy weight with the lowest BMIZ among **Class 5**, and average BMIZ were higher among those exposed to overweight/obesity with the lowest BMIZ among **Class 2**.

Trajectory class-specific adjusted standardized estimates for neonatal body composition outcomes are shown in Table 3 for everyone overall and by BMI category. Generally

adjusted estimates are lower among infants exposed to a healthy prepregnancy BMI and were higher among infants exposed to prepregnancy overweight or obesity. After stratifying by BMI category, **Class 4**—with some initial GWG in early pregnancy and then more moderate rates compared to the other groups—had the lowest fat mass and percent body fat for both the healthy and overweight/obesity prepregnancy BMI categories, while **Class 6** had the highest percent body fat among those infants whose mothers had a healthy prepregnancy BMI and **Class 1** had the highest among infants whose mothers had prepregnancy overweight and obesity. In our sensitivity analyses comparing (1) unadjusted and adjusted and (2) weighted versus highest probability class assignment, neonatal body composition estimates were fairly similar to our primary findings (data not shown).

No significant pairwise differences in neonatal body composition measures were observed overall by integrated prenatal trajectory class (Supplemental Table 6). When stratified by BMI category, among prepregnancy healthy weight (Supplemental Table 6) significant pairwise differences were observed for sum of skinfolds between **Classes 1 & 4** of >1.17 mm and also **Classes 4 & 6** of >1.55 mm, and among infants exposed to prepregnancy overweight/obesity, small pairwise differences in fat-free mass were observed, especially between **Classes 1 & 4** where a difference of over 115 grams was observed and between **Classes 1 & 2** where a difference in fat-free mass index of 0.25 kg/m² was observed (Supplemental Table 6). Results were similar between the weighting and highest probability estimates for pairwise differences with minor differences depending on the covariate adjustment sets (data not shown).

Gestational Diabetes Sensitivity Analysis

A sensitivity analysis was also conducted to examine whether excluding people with gestational diabetes impacted the trajectory patterns and model fit. Exclusion of people with GDM (n=114) from the analytic sample did not substantially change the overall shape or trajectory patterns (Supplemental Figure 1) and did not markedly change model fit. However, there were tighter confidence intervals around the estimates and some differences among certain trajectory groups in regional anthropometric changes were observed. For GWG, estimated first-trimester weight change patterns after exclusion of the GDM cases were somewhat attenuated for **Class 2** and **Class 3**, while the velocity in later pregnancy was somewhat lower for **Class 5**; however, the overall shapes were strikingly similar. For regional anthropometric estimates across gestation, exclusion of GDM cases resulted in lower initial values for MUAC, SSF, and TSF for **Class 2**, but the patterns of change over time were not noticeably different compared to the analytic sample that included participants with GDM.

Discussion

In the first integrative model of time varying changes in multiple measures of anthropometry and adiposity across gestation, we identified six trajectory patterns of co-occurring changes in weight, MUAC, SSF and TSF across gestation, which offers a more nuanced understanding of how these metrics concomitantly change during pregnancy. GWG was modeled jointly with time-varying indicators of subcutaneous adipose tissue in the arm

(TSF), overall upper arm size (MUAC), and subcutaneous adipose tissue changes in the trunk region (SSF). Despite reflecting overall weight changes and regional shifts in adipose tissue depots and circumferences with our trajectory patterns, only a few associations were observed between these trajectory patterns with neonatal body composition measures.

Our best fitting model included six trajectory patterns for GWG and body composition across gestation with some curves showing high initial GWG in the first trimester and others showing initial weight loss, stability or low GWG and then varying rates in the second and third trimesters. The shapes of the GWG curves were relatively similar across the BMI categories with more marked differences between some groups earlier in pregnancy. As expected, there was lower overall GWG among those with overweight or obesity, while MUAC, SSF and TSF by prenatal trajectory classes were more overlapping with each other among those with prepregnancy overweight or obesity. The concomitant changes in weight and body composition patterns as depicted show interesting relationships that appear to be differential by prepregnancy BMI category. For example, for **Class 5**, weight loss and then accelerated weight gain was observed among both BMI groups, and this shift in weight is reflected in initial stability and then increases in MUAC, and also increases and then a plateau in both SSF and TSF among those with healthy weight, whereas the body composition shifts among those with prepregnancy overweight and obesity are much less striking for MUAC and TSF and only the SSF seems to notably increase. For **Class 4**, the low GWG observed in the first trimester among those with healthy prepregnancy BMI is also observed among those with overweight and obesity, but remains low well into the 2nd trimester. This difference is also reflected in the body composition parameters; increases are seen for SSF and TSF across pregnancy among those with healthy weight in **Class 4**, reflecting adipose tissue deposition, while decreases in SSF and TSF across gestation in **Class 4** were observed among people with overweight or obesity, reflecting mobilizing of adipose tissue.

It is unknown how each of the six integrated prenatal trajectory groups reflect the uterine metabolic environment and nutritional availability to support fetal growth. We theorized that patterns characterized by high GWG and gains in skinfold thickness in the trunk region (such as subscapular) in early pregnancy may reflect a less favorable metabolic milieu and indicate greater fuel availability in early pregnancy that may promote excessive adiposity accrual in the fetus, particularly among people with obesity.^{16, 29} Patterns characterized by relatively low GWG or weight loss in early pregnancy—and smaller increases, stability or decreases in skinfolds and mid-upper arm circumference—may reflect a more favorable early pregnancy metabolic milieu; however, those with higher adiposity levels in early pregnancy may still have insulin resistance and elevated lipids/triglycerides despite showing lower GWG or even weight loss at this time.

Overall, despite our predictions, the prenatal trajectories were not associated with pairwise differences between neonatal body composition outcomes. After stratifying by pregnancy BMI category, a few differences between prenatal trajectory classes were observed for skinfold thickness among those infants whose mothers had prepregnancy normal weight and for fat-free mass among infants of mothers with prepregnancy overweight/obesity, and no significant pairwise differences were found for fat mass, BMIZ or percentage body fat

in contrast to our hypothesis. This lack of differences in most neonatal body composition measures suggests that GWG patterns—even those with very rapid and high GWG and increases in regional adipose tissue depots and circumferences—may not impact neonatal body composition as strongly within similar prepregnancy adiposity levels, or when GWG modeling also incorporates prenatal regional body composition changes. It also could be due our relatively healthy sample compared to the general population due to strict inclusion criteria for the FGS. Interestingly, significant pairwise differences in both BMI strata were observed between **Class 1** and **Class 4** but for different measures; higher values in **Class 1** compared to **Class 4** were observed for skinfold thickness among infants of mothers with healthy prepregnancy weight and for lean mass among infants for infants in the overweight/obesity prepregnancy BMI category. The differences in GWG and body composition between Classes 1 & 4 are apparent in the first trimester, where Class 1 has relative weight stability and Class 4 shows low GWG, and then as pregnancy progresses more rapid increases in Class 1 in GWG and body composition measures, compared to Class 4, suggesting this period of rapid GWG after weight stability may propagate higher subcutaneous adipose tissue accumulation in infants born to individuals with prepregnancy normal weight, while among infants born to individuals with prepregnancy overweight/obesity this may lead to greater neonatal lean mass, but interestingly not greater fat mass. Previous reports from the NICHD FGS in which low GWG and moderate-high GWG trajectories estimated with latent class analyses (i.e., proc traj in SAS with polynomials to capture the shape of the curve over time) were positively associated with LGA, a crude indicator of larger body size at birth,¹¹ are in contrast to our limited pairwise differences in neonatal body composition using the joint prenatal model. While this approach was similar to our latent class analysis, we jointly modeled weight with other measures of adiposity and body size changes, used splines for curve estimation to capture the nuanced shape of the changes, and we examined neonatal body composition rather than using a larger size-for-gestational age.

Our results are generally consistent with the prior literature showing distinct patterns of GWG and body composition change across pregnancy and further that some GWG trajectory patterns are associated with neonatal size and body composition outcomes. Although analyses incorporating GWG and body composition into a joint trajectory model have not been fit previously, others have reported on correlations or associations between individual prenatal anthropometric measures with newborn anthropometry or fat mass estimated with equations.^{13, 14} In one study, small positive correlations between maternal fat mass with infant biceps, triceps, iliac crest and subscapular skinfold measures were observed.³⁰ In another study from NICHD FGS participants with a BMI < 30 kg/m², higher rates of change in maternal MUAC and triceps skinfolds were associated with lower lean mass, but not fat mass.¹³ We have previously reported on how the pattern of GWG by trimester was associated with overall body composition changes across pregnancy, and also with neonatal birthweight in a 1990s New York-based cohort. Among pregnant individuals (n=156) with predominately healthy weight prepregnancy BMI (60.3%), higher GWG rates were associated with greater overall fat mass gains across pregnancy, and also with greater neonatal birth weight and length.⁹ Our findings build upon this work by showing concomitant shifts in regional body composition measures along with GWG, and that

high GWG is reflected in these regional body composition changes. For GWG patterns in relation to neonatal adiposity, in a Colorado-based birth cohort (n=752) in which about half of participants had a healthy weight prepregnancy BMI (52%), a quarter had overweight (25%) and a fifth had obesity (20%), high rates of GWG in early (0–17 weeks), mid (17–27 weeks), and late gestation (>27 weeks) estimated with multiple linear regression were positively associated with neonatal adiposity and percentage body fat assessed with air-displacement plethysmography.¹² In this cohort, a 1-kg/week increase in early, mid, and late pregnancy GWG was associated with an estimated 8.12, 9.1, and 6.2 g higher neonatal fat mass and 0.18, 0.21, and 0.13 higher neonatal percentage body fat, respectively.¹² These findings are in contrast to ours, as we found no associations between integrated prenatal trajectories with neonatal adiposity measures other than skinfold thickness for those with prepregnancy healthy weight; this could be because we used a very different modeling approach with our latent class analysis incorporating prenatal body composition and weight, and different infant body composition measures (skinfolds/anthropometry vs. air-displacement plethysmography).

Sensitivity analyses were conducted to examine whether exclusion of GDM cases markedly changed trajectory class shapes and model fit. Exclusion of GDM cases from the joint model did not markedly change the shape of the GWG curves, which was not surprising given our small sample size of GDM cases.

Due to the scope of the study, we were unable to assess overall body composition changes (i.e., fat and fat free mass) with a multi-compartment method or with MRI in our pregnant participants, and were only able to use regional assessments of adiposity with skinfold thickness and anthropometric changes in weight and mid-upper arm circumference. Although there do exist some equations for estimating prenatal fat mass change during pregnancy, we are unaware of an equation that would be appropriate for estimating change in adiposity across pregnancy with data similar to ours, and further, use of the absolute skinfold thickness values for examining data longitudinally is preferred as it applies fewer assumptions to the data.³¹ While neonatal body composition was estimated with validated prediction equations using skinfold thickness and circumferences, it was not measured with a multi-compartment model. Neonatal measures were conducted 12–24 hrs after birth and water loss and other body composition changes during this period could potentially have impacted the accuracy of our measurements; however, given that the infants in NICHD FGS were all measured around the same time window post-delivery, and that we have not seen other reports of prenatal weight and body composition changes during pregnancy impacting these changes, we are unsure how this would affect our findings. Compared to those not included in our analysis, our analytic sample was of higher socio-economic status, which may affect the generalizability of our findings. Additionally, our ability to detect associations and our generalizability is also affected by the strict inclusion criteria for the NICHD-FGS resulting in a healthier sample with no chronic disease among those with healthy and overweight prepregnancy BMI and less chronic diseases among those with obesity, compared to the general prenatal population. However, we hypothesize that if this analysis were repeated in a more general obstetric population, greater variance in our neonatal body composition measurements would likely have been observed and allowed more discrimination among the prenatal trajectories. While infant BMIZ scores

in our sample were lower than the WHO reference population (i.e., values below 0), our sample still had a high prevalence (53.2%) of those with excessive GWG, which is in line with prevalence data from the United States showing a range of excessive GWG from 38.2–54.7%, depending on the state.³ Our prepregnancy BMI was calculated from self-reported prepregnancy weight, but was highly correlated with measured prepregnancy weights in the NICHD FGS and has also been shown to be highly correlated in other populations.³² Prenatal weights used in our trajectory modeling were from both study visits and routine prenatal care, therefore there may be variability in the time of day and fasting status when measurements were taken; pregnancy measures taken later in the day may also be affected by water retention/edema. Additionally, we presented results with predicted probabilities and also assigning participants to the trajectory class with the highest probability, and noted more greater divergence of estimates between weighted vs. highest class membership assignment for the classes with smaller numbers. Despite these limitations, this analysis is strengthened by the study design. The NICHD FGS—Singletons is a contemporary, diverse longitudinal cohort with repeated measurements of prenatal regional body composition measurements at up to six time points during pregnancy along with neonatal body composition anthropometric measurements obtained by highly trained research personnel.

Conclusions

Six trajectory patterns of prenatal weight, anthropometry and body composition change across pregnancy were identified, allowing for a more nuanced understanding of GWG and regional body composition changes co-occurring across pregnancy. These patterns were minimally associated with neonatal body composition, which was more strongly linked to prepregnancy BMI category. This paper provides an example of an analytic approach that integrates complex time-varying data and multiple measures of adiposity across gestation into a single exposure per individual. This type of analytic approach can be used to integrate multiple measures to contextualize the uterine environment in epidemiologic research to better predict risks and also inform interventions. These types of dynamic integrative models can also possibly be leveraged for future personalized interventions designed to support healthy GWG and nutrition during pregnancy, which could for example incorporate real-time assessment of weight and body composition coupled with prenatal diet, activity, and metabolic measures in order to guide recommendations. Although few differences in neonatal body composition by prenatal trajectory group were observed, we did observe some small differences for skinfold thickness and lean mass, and moreover, observed differences in neonatal body composition by BMI strata with higher values among infants born to individuals with prepregnancy overweight or obesity. Given that children's body composition may track across childhood and into adulthood, supporting pregnant individuals and people planning pregnancy to have a healthy BMI along with appropriate GWG may have lasting implications for offspring size.^{15, 33, 34}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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EMW conceptualized, designed and led this study and has primary responsibility for the content; JG and CZ are intramural PIs for the NICHD FGS; RW, DW, JO, DWS, ACR, RN, WG are site PIs for NICHD FGS study sites; CN provided didactic training to EMW on fetal growth and body composition; NB, MD and EW developed the analytic method; NB, GB, MD conducted data analyses; EMW, NB, ARN, RR, SSF, LGK, MD interpreted the results. All authors contributed to the manuscript drafting, editing, and approve of the final manuscript. The authors also thank Sara Dube at the University of Texas at Austin for her assistance with the manuscript tables.

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Data Sharing:

Data described in the manuscript will be made available upon request pending application and approval from NICHD. Analytic code will be available from the first author upon request pending application and approval.

Abbreviations:

| | |
|-------------|--------------------------------|
| FGS | Fetal Growth Studies |
| GWG | gestational weight gain |
| IOM | Institute of Medicine |
| MUAC | mid-upper arm circumference |
| SSF | subscapular skinfold thickness |
| TSF | triceps skinfold thickness |

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Prenatal measurements across gestation

| | 8-13 wk | 16-22 wk | 24-29 wk | 30-33 wk | 34-37 wk | 38-41 wk |
|------------------|---------|----------|----------|----------|----------|----------|
| Skinfolds | X | X | X | X | X | X |
| Circumferences | X | X | X | X | X | X |
| Prenatal weights | —————→ | | | | | |

Latent Class Trajectory Model

Joint trajectories incorporating
Individual GWG & skinfold thicknesses & circumference measures

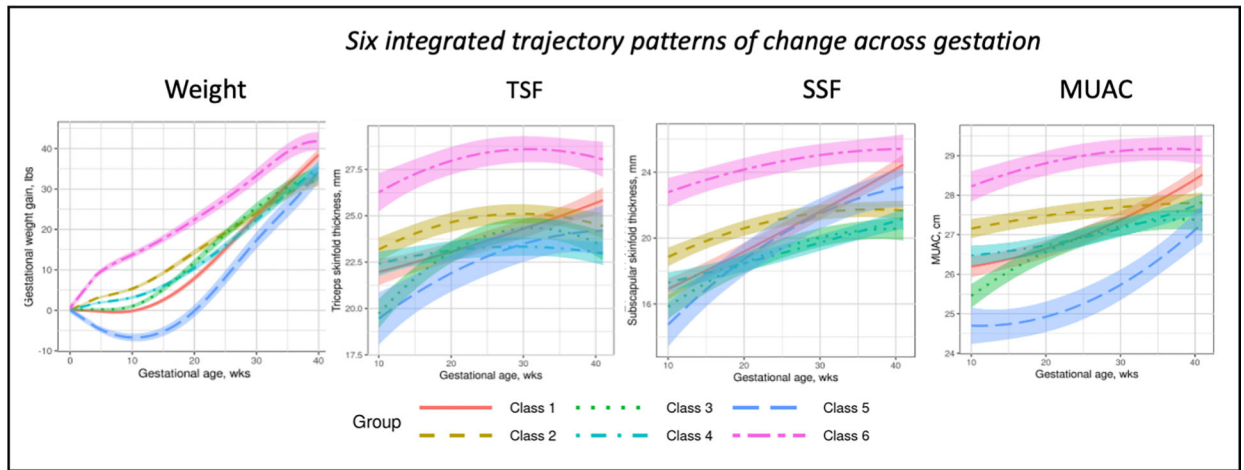
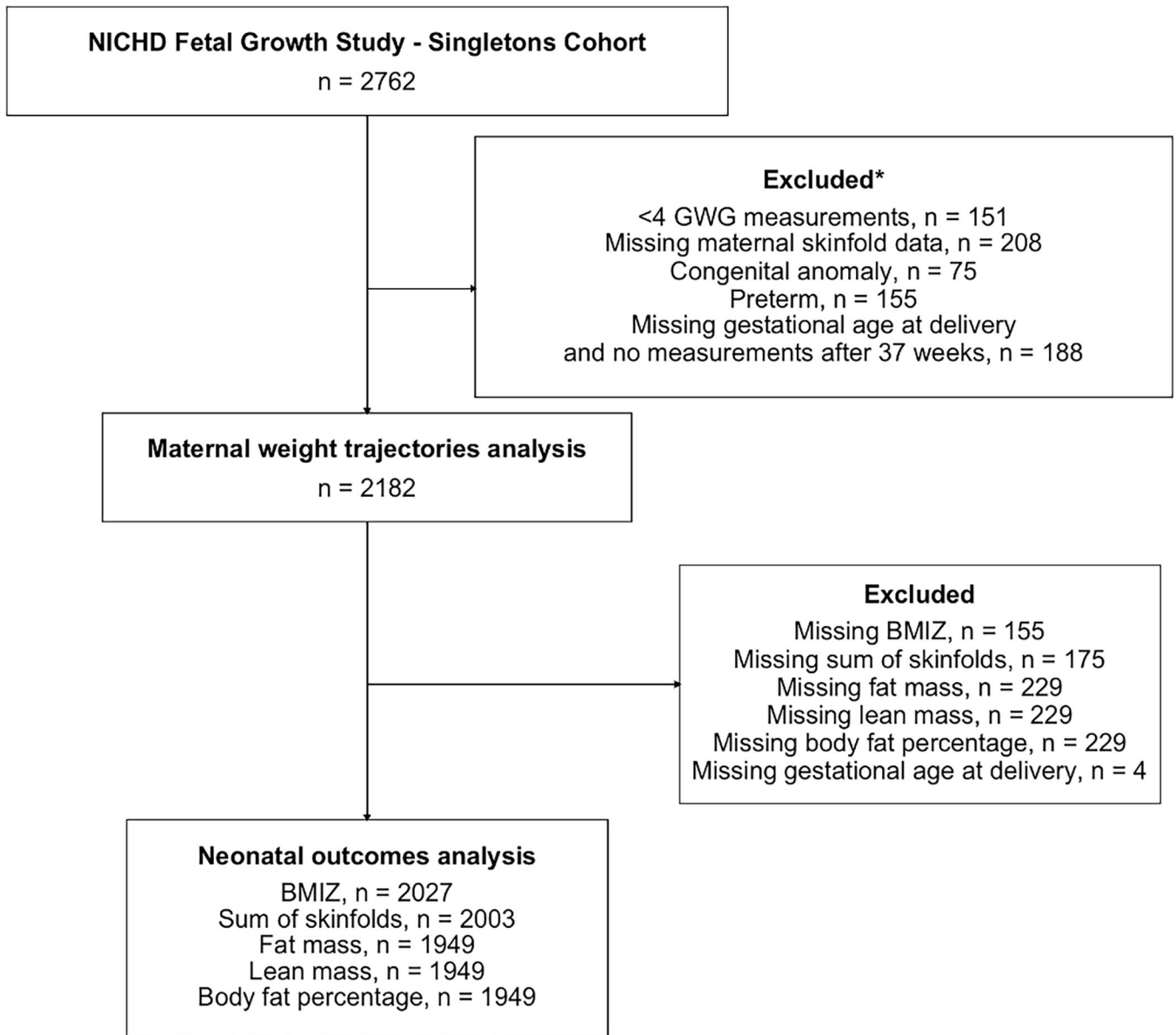


Figure 1. Visual overview of prenatal data measurement timing and integration into the joint latent trajectory model. Overview shows an example of the six latent trajectory change pattern estimates and 95% confidence intervals across pregnancy for the healthy weight BMI category reflecting dynamic patterns of change for each of the measures.

**Figure 2.**

Participant flow diagram of the prenatal weight and body composition trajectory and neonatal body composition analysis, NICHD Fetal Growth Studies

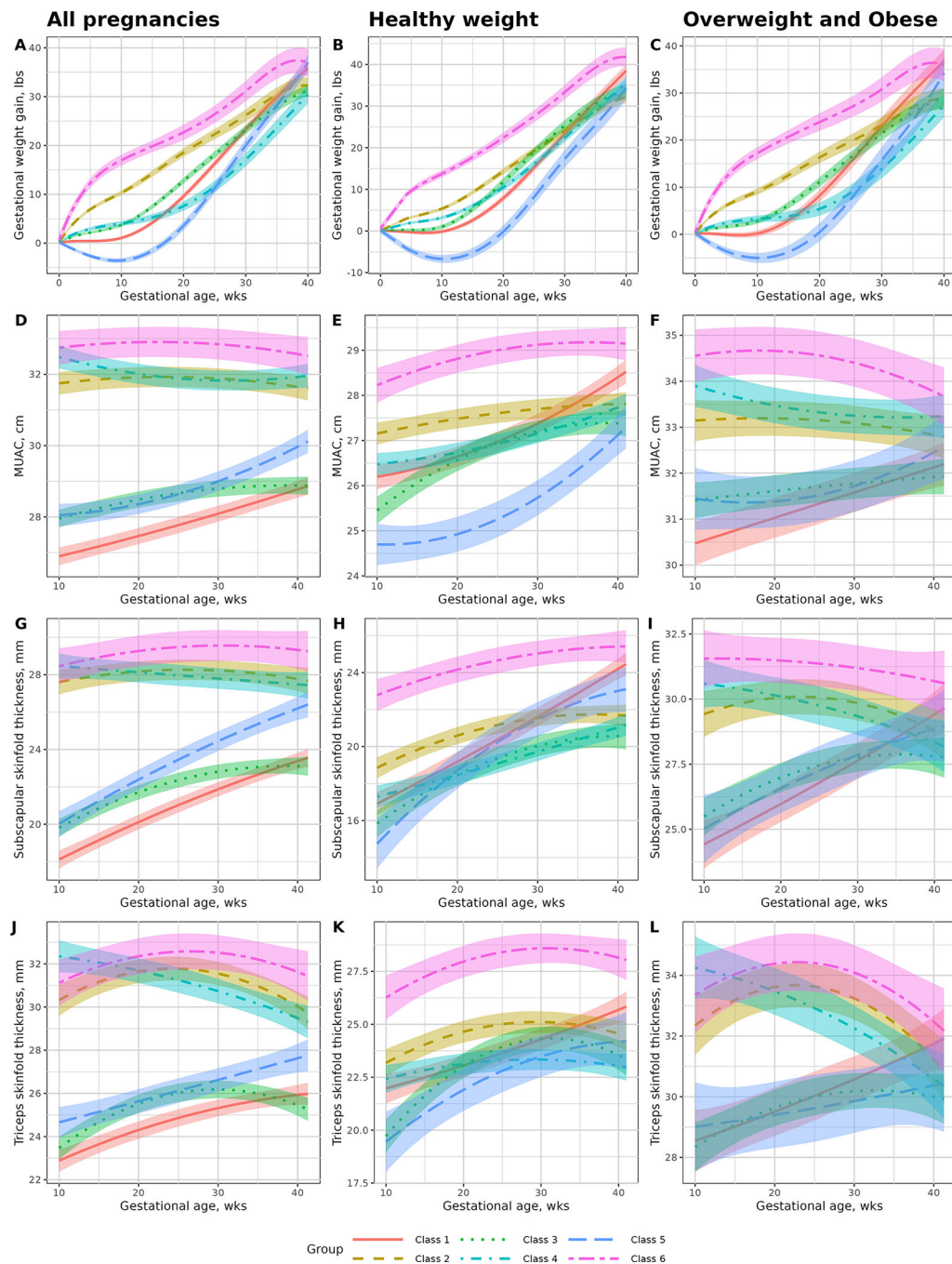


Figure 3.

Estimated GWG and regional body composition trajectories across gestation and 95% confidence intervals overall and by prepregnancy BMI category, NICHD Fetal Growth Studies (Overall n=2182; Healthy weight n=1242; Overweight/obesity BMI n=940). GWG and body composition trajectories were fit with a joint latent class model including prenatal weight, MUAC, SSF, TSF into an integrated model, adjusting for prepregnancy BMI. MUAC, mid-upper arm circumference.

Table 1. Participant characteristics by GWG-body composition trajectory class, NICHD Fetal Growth Studies among all participants included in the analysis (n=2182)

| | GWG-body composition trajectory class | | | | | | |
|--|---------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | All (n=2182) | Class 1 (n=640) | Class 2 (n=293) | Class 3 (n=599) | Class 4 (n=258) | Class 5 (n=283) | Class 6 (n=109) |
| Prenatal | | | | | | | |
| Age, y | 28.5±0.1 | 28.3±0.2 | 29.4±0.3 | 29.9±0.2 | 27.9±0.3 | 25.9±0.3 | 27.7±0.5 |
| Education > high school, % | 73.3 | 76.3 | 71.7 | 79.1 | 68.2 | 64.0 | 65.1 |
| Income >= \$50,000, % | 57.9 | 64.2 | 48.8 | 69.5 | 48.7 | 42.4 | 40.0 |
| Married or cohabitating, % | 78.0 | 81.1 | 77.1 | 83.6 | 73.5 | 67.7 | 68.8 |
| Height, cm | 162.5±0.1 | 162.3±0.3 | 162.2±0.4 | 161.9±0.3 | 163.2±0.4 | 163.7±0.4 | 163.2±0.7 |
| Parity prior to index pregnancy > 0, % | 53.1 | 47.8 | 68.6 | 54.3 | 56.2 | 42.4 | 56.9 |
| GDM during pregnancy, % | 5.0 | 0.9 | 13.3 | 5.7 | 5.8 | 2.1 | 9.2 |
| Gestational age at delivery, wk | 39.5±0.02 | 39.5±0.04 | 39.4±0.06 | 39.6±0.04 | 39.5±0.07 | 39.5±0.07 | 39.3±0.11 |
| Race/Ethnicity | | | | | | | |
| Non-Hispanic White | 29.7 | 32.8 | 19.1 | 35.1 | 29.8 | 25.1 | 21.1 |
| Non-Hispanic Black | 22.1 | 18.8 | 31.7 | 15.4 | 28.3 | 23.7 | 34.9 |
| Asian-Pacific Islander | 17.7 | 22.5 | 14.3 | 20.7 | 9.3 | 15.5 | 7.3 |
| Hispanic | 30.5 | 25.9 | 34.8 | 28.9 | 32.6 | 35.7 | 36.7 |
| Neonatal | | | | | | | |
| Female sex, % | 48.8 | 47.9 | 53.4 | 47.1 | 44.4 | 52.3 | 53.2 |
| Birthweight, g | 3344±10 | 3321±18 | 3332±25 | 3330±43 | 3351±30 | 3367±16 | 3358±30 |
| BMI Z-score | -0.19±0.02 | -0.24±0.05 | -0.17±0.06 | -0.15±0.04 | -0.22±0.08 | -0.15±0.07 | -0.21±0.10 |
| Sum of skinfolds, mm | 20.0±0.1 | 19.9±0.2 | 20.6±0.3 | 19.6±0.2 | 20.6±0.4 | 19.9±0.3 | 20.8±0.6 |
| Fat mass, g | 428±4 | 417±7 | 431±10 | 428±6 | 443±12 | 435±10 | 424±17 |
| Fat mass index, kg/m ² | 1.69±0.01 | 1.65±0.03 | 1.70±0.04 | 1.69±0.03 | 1.74±0.05 | 1.71±0.04 | 1.68±0.07 |
| Fat free mass, g | 2931±7 | 2919±12 | 2915±17 | 2946±12 | 2935±20 | 2958±21 | 2898±33 |
| Fat free mass index, kg/m ² | 11.57±0.02 | 11.54±0.03 | 11.54±0.05 | 11.58±0.03 | 11.56±0.05 | 11.65±0.05 | 11.48±0.08 |
| Body fat percent, % | 12.4±0.1 | 12.2±0.2 | 12.6±0.2 | 12.5±0.4 | 12.7±0.3 | 12.4±0.1 | 12.5±0.2 |
| LGA, % | 9.4% | 8.7% | 8.3% | 8.9% | 10.1% | 11.5% | 11.1% |
| SGA, % | 8.1% | 9.1% | 5.5% | 5.4% | 11.7% | 10.8% | 8.3% |

Values are mean±SE or %. Class specific demographics and characteristics are shown in Table 1 and are the estimated means based on the weighted least squares models and their corresponding standard errors. Data available for subsets of participants for the following covariates: income (n=1887), marital status (n=2180), height (n=2167), gestational age at delivery (n=2160), sex (n=2161), neonatal BMI z-score (n=2027), neonatal sum of skinfolds (n=2007), neonatal fat/lean mass and % fat (n=1953), LGA/SGA (n=2154).

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Table 2. Characteristics of the six GWG-body composition trajectory classes among the overall sample, NICHD Fetal Growth Studies (n=2182)

| | GWG-body composition trajectory class | | | | | | |
|---|---------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | All (n=2182) | Class 1 (n=640) | Class 2 (n=293) | Class 3 (n=599) | Class 4 (n=258) | Class 5 (n=283) | Class 6 (n=109) |
| Proportion of participants | - | 29.3% | 13.4% | 27.5% | 11.8% | 13.0% | 5.0% |
| Prepregnancy BMI, kg/m ² | 25.3±0.10 | 23.2±0.1 | 27.7±0.3 | 24.0±0.2 | 29.2±0.4 | 25.4±0.3 | 28.4±0.5 |
| Prepregnancy BMI category, % | | | | | | | |
| Healthy weight (18.5–24.9 kg/m ²) | 56.9 | 75.5 | 32.8 | 67.1 | 27.1 | 55.8 | 30.3 |
| Overweight (25.0–29.9 kg/m ²) | 26.7 | 19.8 | 38.9 | 24.0 | 32.9 | 27.2 | 33.0 |
| Obese (>30.0 kg/m ²) | 16.4 | 4.7 | 28.3 | 8.8 | 39.9 | 17.0 | 36.7 |
| Adherence to IOM Guidelines ¹ , % | | | | | | | |
| Inadequate GWG | 17.0 | 15.1 | 13.5 | 19.9 | 16.4 | 21.9 | 11.0 |
| Excessive GWG | 53.2 | 52.2 | 62.3 | 42.6 | 56.6 | 59.0 | 68.8 |
| Total GWG, lb | 32.5±0.3 | 35.8±0.6 | 32.3±0.8 | 31.2±0.6 | 30.4±0.9 | 37.0±0.9 | 36.9±1.4 |
| Model estimated weekly weight change (lb/wk) by trimester | | | | | | | |
| 1 st Trimester | - | 0.20 | 0.97 | 0.44 | 0.36 | -0.21 | 1.44 |
| 2 nd Trimester | - | 1.18 | 0.80 | 1.03 | 0.64 | 1.25 | 0.67 |
| 3 rd Trimester | - | 1.28 | 0.66 | 0.85 | 1.29 | 1.71 | 0.67 |
| Overall anthropometry across gestation | Intercept | Slope | Quadratic | | | | |
| MUAC, cm (Estimate (SE)) | 28.7 (0.02) | 1.3 (0.4) | 0.0 (0.3) | | | | |
| TSF, mm (Estimate (SE)) | 23.9 (0.4) | 9.5 (1.3) | -6.1 (1.1) | | | | |
| SSF, mm (Estimate (SE)) | 20.1 (0.4) | 8.1 (1.2) | -3.1 (1.0) | | | | |

¹IOM Guideline adherence calculated by using total weight gain with last measured weight prior to delivery in participants with last measured weights within 3 wk of delivery (n=1944). BMI, body mass index; GWG, Gestational weight gain; MUAC, mid-upper arm circumference; TSF, triceps skinfold thickness; SSF, subscapular skinfold thickness. Mean±SE all such values. Total GWG estimates by class derived from model estimates.

Adjusted GWG-body composition trajectory class-specific estimated neonatal size outcomes overall and by BMI category

Table 3.

| | GWG-body composition trajectory class | | | | | |
|---|---------------------------------------|------------|------------|------------|------------|------------|
| | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 |
| Everyone (n=2027) | | | | | | |
| BMIz | -0.12±0.05 | -0.17±0.07 | -0.15±0.05 | -0.31±0.08 | -0.11±0.07 | -0.27±0.12 |
| SSF, mm | 20.5±0.2 | 20.2±0.4 | 19.9±0.2 | 20.2±0.4 | 20.1±0.3 | 20.2±0.7 |
| Fat mass, g | 439±8 | 428±11 | 427±7 | 430±14 | 442±10 | 408±20 |
| Fat mass index, kg/m ² | 1.73±0.03 | 1.69±0.04 | 1.68±0.03 | 1.69±0.05 | 1.73±0.04 | 1.62±0.08 |
| Lean mass, g | 2949±12 | 2928±18 | 2934±12 | 2908±22 | 2974±20 | 2890±35 |
| Lean mass index, kg/m ² | 11.61±0.04 | 11.57±0.05 | 11.57±0.04 | 11.51±0.06 | 11.66±0.05 | 11.45±0.09 |
| % fat | 12.6±0.2 | 12.5±0.3 | 12.4±0.2 | 12.5±0.3 | 12.6±0.2 | 12.1±0.5 |
| Healthy BMI (n=1150) | | | | | | |
| BMIz | -0.22±0.07 | -0.25±0.06 | -0.32±0.08 | -0.33±0.07 | -0.21±0.15 | -0.36±0.12 |
| SSF, mm | 20.2±0.3 | 19.0±0.3 | 19.4±0.3 | 18.9±0.3 | 19.1±0.7 | 20.5±0.6 |
| Fat mass, g | 417±10 | 405±9 | 408±10 | 389±9 | 418±20 | 431±17 |
| Fat mass index, kg/m ² | 1.66±0.04 | 1.62±0.04 | 1.59±0.04 | 1.56±0.04 | 1.65±0.09 | 1.68±0.07 |
| Lean mass, g | 2915±20 | 2897±16 | 2930±18 | 2875±16 | 2937±31 | 2917±31 |
| Lean mass index, kg/m ² | 11.58±0.05 | 11.55±0.05 | 11.47±0.06 | 11.50±0.05 | 11.61±0.10 | 11.41±0.08 |
| Percent body fat, % | 12.3±0.2 | 12.0±0.2 | 11.9±0.2 | 11.6±0.2 | 12.2±0.5 | 12.6±0.4 |
| Overweight or Obesity Prepregnancy BMI (n=877) | | | | | | |
| BMIz | 0.05±0.10 | -0.15±0.08 | -0.09±0.07 | -0.26±0.11 | 0.13±0.15 | -0.01±0.12 |
| SSF, mm | 21.1±0.5 | 21.3±0.4 | 20.6±0.3 | 20.9±0.5 | 21.0±0.6 | 20.9±0.7 |
| Fat mass, g | 478±15 | 441±13 | 446±11 | 439±18 | 474±24 | 458±20 |
| Fat mass index, kg/m ² | 1.86±0.06 | 1.73±0.05 | 1.74±0.04 | 1.74±0.07 | 1.83±0.09 | 1.81±0.08 |
| Lean mass, g | 3032±24 | 2934±20 | 2960±17 | 2904±27 | 3032±50 | 2947±34 |
| Lean mass index, kg/m ² | 11.77±0.07 | 11.52±0.06 | 11.59±0.05 | 11.53±0.08 | 11.82±0.11 | 11.62±0.09 |
| Percent body fat, % | 13.4±0.3 | 12.7±0.3 | 12.7±0.2 | 12.7±0.4 | 13.1±0.5 | 13.2±0.4 |

Values are mean±SE. Standardized estimates are derived from weighted least squares for each class, adjusting for race, gestational age at delivery, prepregnancy BMI and parity for all models, and infant sex for all models other than BMI z-score. Each participant was assigned to the highest probability class. Sum of skinfolds (SSF) includes the sum of abdominal flank, anterior thigh, triceps, and subscapular skinfold thickness. BMIz (n=2027), SSF (n=2007), Fat mass, lean mass & % fat (n=1953).