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Original Research Article

Infant body composition trajectories differ by in utero exposure to gestational diabetes mellitus: a prospective cohort from birth to 12 months

Rachel R Rickman [1], Elizabeth M Widen [1,*], Charlotte E Lane [2], Marcela R Abrego [1], Amy R Nichols [1], Saralyn F Foster [1], Patrick Catalano [3]

[1] *Department of Nutritional Sciences, The University of Texas at Austin, Austin, TX, United States;* [2] *Food Security Evidence Brokerage, Ithaca, NY, United States;* [3] *Division of Reproductive Endocrinology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States*

A B S T R A C T

Background: Infants exposed to gestational diabetes mellitus (GDM) in utero are known to have higher fat mass (FM) and less fat-free mass (FFM) at birth, but little is known about how their adiposity changes over the first year of life.
Objectives: We identified growth and body composition patterns across the first year and evaluated for differences by GDM exposure status.
Methods: Among 198 infants (52% GDM exposed), growth and body composition with total body electrical conductivity were obtained from birth to 1 y. Latent class mixed modeling (LCMM) trajectories were fit for weight-, length-, and body mass index (BMI)-for-age World Health Organization *z*-scores, as well as percent body fat, FM, and FFM. Adjusted associations between GDM with trajectory classes were evaluated with multiple logistic regression.
Results: At birth, infants exposed to GDM had higher FM, higher percent body fat, and a higher BMI compared with infants unexposed. A larger proportion of infants exposed to GDM were classified into LCMM growth trajectory classes that experienced less FM (67% GDM exposed) and percent body fat gain (79% GDM exposed), compared with the other classes (X^2 *P* values <0.05). In adjusted models, infants exposed to GDM were 69% less likely (Relative Risk Ratios (RRR) = 0.39, 95% confidence interval: 0.11, 0.82) to belong in the highest FM trajectory that reached 4 kg of FM at 1 y of age. In adjusted models, GDM exposure was not associated with FFM, weight-, length-, or BMI-for-age trajectories.
Conclusions: In a cohort of infants exposed and unexposed to GDM in utero, infants exposed had increased weight, FM, and percent body fat at birth. However, more infants exposed to GDM had less fat accrual over the first year of life, compared with those unexposed. The long-term effects of these growth patterns in the first year challenge current concepts and support further investigation of neonatal body composition.

Keywords: GDM exposed, infant growth, body composition, nutritional epidemiology, infant growth epidemiology, infant growth trajectories, catch-down growth, total body electrical conductivity

Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing worldwide in the past 20 y [1–3]. Pregnant females are more likely to be diagnosed with GDM if they have a family history of diabetes mellitus, are older in age, or have a higher BMI (in kg/m^2) [4–7]. Growth in the first year of life is known to influence overweight and obesity status later in life. Specifically, rapid infancy weight gain is associated with becoming classified with overweight or obesity in toddlerhood and childhood [8–10]. Birthweight of infants exposed to GDM in utero is higher than infants unexposed to GDM [11]. This also varies by race as non-Hispanic White infants exposed to GDM in utero have lower birthweights compared with other racial/ethnic groups [12] and may suggest differential care or other factors that influence the birth effects of GDM. However, the use of weight alone to assess the effects of GDM on infant growth and development does not reflect possible variation in adiposity independent of weight [13].

GDM has been linked to long-term adiposity in early infancy and mid-childhood [14]. Others have shown that GDM exposure is associated with increased offspring adiposity using skinfolds at 3 y of age [15], overweight status at 7 y of age [11], and high BMI, hip, and waist circumferences at a mean age of 9 y [16]. Infants born large for gestational age (LGA; birthweight >90th percentile) exposed to GDM in utero are at an increased risk of having excess fat mass (FM),

Abbreviations: AGA, average for gestational age; FFM, fat-free mass; FM, fat mass; GCRC, General Clinical Research Center; GDM, gestational diabetes mellitus; LCMM, latent class mixed modeling; LGA, large for gestational age; TOBEC, total body electrical conductivity.

* Corresponding author.
E-mail address: elizabeth.widen@austin.utexas.edu (E.M. Widen).

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increased percent body fat, and less fat-free mass (FFM; muscle, bone, etc.) at birth compared with LGA infants not exposed to GDM [17]. Infants exposed to GDM have an increased risk of excess FM at birth even when born at average size for gestational age (AGA) [18]. This pattern of increased adiposity in infants exposed to GDM has been shown to persist to 6 mo of age [19].

How GDM exposure differentially impacts patterns of growth from birth to 6 mo and whether GDM differentially is associated with adipose tissue changes in the second 6 mo is unknown. Catch-down growth can also take place during the first 2 y of an infant's life, including those exposed to GDM in utero, and may be the result of faster antenatal growth than true to their own genetic growth potential essentially causing infants to slow their growth to match the curve they genetically would be expected to grow [20,21]. This is usually seen as a shift down in growth percentiles over the first 2 y of life [22].

Among infants not exposed to GDM, few studies have assessed change in body composition longitudinally in children [23] and from birth through 1 y [24,25] with 2- or multicompartment methods assessing both FM and FFM. Methods to assess overall FM and FFM in infants require radiation exposure (dual-energy X-ray absorptiometry) or only fit infants ≤8 kg such as air displacement plethysmography [26]. Other methods that can be used for repeated measures without radiation include quantitative magnetic resonance, which is not widely available, or total body electrical conductivity (TOBEC), which is no longer available clinically but was during the duration of the current study [27]. Strikingly no studies have conducted repeated assessments of adiposity among infants exposed to GDM in utero.

Therefore, we sought to compare growth and body composition patterns of infants exposed to GDM in utero and those unexposed across the first year of life. We leveraged an advanced analytic technique, latent class mixed modeling (LCMM), to provide insight about different features of growth. We hypothesized that growth and body composition patterns will differ by GDM exposure with infants exposed to GDM showing higher FM and lower or similar FFM at birth. We also expected that infants exposed to GDM will experience faster weight and FM gain, but similar linear growth and FFM gain as infants unexposed.

Methods

Data are from a prospective observational cohort conducted at The MetroHealth System in Cleveland, Ohio. The purpose of the study was to document the longitudinal changes in body composition in infants with in utero GDM exposure and normal glucose tolerance. This secondary analysis leverages advanced statistical modeling methods to examine the role of GDM on body composition and growth in this cohort. Recruitment was conducted in the postpartum unit and included infants born from 1990 to 2006; a majority (68%) were recruited prior to 1996 with additional participants recruited until reaching 200 participants in 2006. Participants were invited to partake in the study if they had a singleton pregnancy, had a term birth (> 37 wk estimated gestational age), their infants had no birth anomalies, and their infants were admitted to the newborn nursery and not a neonatal intensive care unit as they would be unable to participate in TOBEC for the birth visit. In total, 201 infants were recruited to participate. Three were excluded for preterm births resulting in 198 infants included in the analytic sample.

Maternal measurements

At baseline, a number of characteristics were collected by trained staff (research nurses in the clinical research unit) including GDM status which was based on the method of Carpenter and Coustan (the clinical definition of GDM at the institution at the time of the study) [28], parity (classified as first pregnancy or not), race (self-identified as Hispanic, non-Hispanic White, Asian American, or Other), smoking status during pregnancy, and education (classified by no college or some college or higher). Other variables were extracted from medical charts including prepregnancy BMI, height (inches), gestational weight gain (kilograms gained from prepregnancy weight to weight at last prenatal visit), mode of delivery (vaginal compared with C-section), and gestational age of infant at birth (classified by last menstrual period confirmed by early gestational age ultrasound). This study took place in a single clinic. The clinic followed a protocol for GDM treatment including a GDM diet (50% complex carbohydrate, 20% protein, and 30% fat) and increased physical activity. Insulin was the only medication to treat GDM not responsive to dietary changes. No metformin or glyburide was given to the pregnant females during their pregnancy.

Infant measurements

Infant body composition measurements were completed by trained staff at all in-person infant study visits in the General Clinical Research Center (GCRC) at MetroHealth Medical Center (RR-00080). Infants were brought to the GCRC for phenotyping visits at birth (within 72 h), 4 mo, 8 mo, and 12 mo of age. All infants had to have ≥2 of the 4 in-person visits completed to be included in the analytic sample with an average of 3.3 visits (range 2–4). Nonparticipation at a visit was due to aging out of the 4-, 8-, and 12-mo follow-up time period. At these visits, weight was measured on a calibrated electronic scale, length was assessed using a recumbent length board, and TOBEC (resulting in FM, FFM, and percent body fat) was conducted.

TOBEC is a bioelectrical technique that measures TOBEC by placing the participant through a 2.5-MHz coil electromagnetic field [29]. As the participant moves through the field, they absorb heat energy and the instrument can detect the mass of the body distinguishing FM and FFM [30]. Body composition has been previously measured using TOBEC [31–33] and specifically with infants exposed to GDM in utero [17,18,34–36]. There are strengths of using TOBEC for this study including being able to use the same methodology for all anthropometric visits (across all ages) and having no radiation exposure as with dual-energy X-ray absorptiometry. It is also not affected by hydration as with bioimpedance analysis, and there was a high acceptance by parents in this study as none refused.

Small for gestational age (birthweight <10th percentile), LGA, and AGA were calculated from birth charts developed for this hospital from the 1990s [37]. Growth measurements were assessed for biological implausibility (i.e., loss in length) using growth curves. Infant BMI was calculated using the standard formula: body weight (kg)/length $(m)^2$. We calculated all WHO z-scores using the zanthro command in Stata [38]. These WHO z-scores included length-for-age, weight-for-age, and BMI-for-age.

Infant BMI trajectories have been associated with later risk for adolescent overweight/obesity. We elected to use the BMI trajectories rather than WHO weight-for-length z-scores [39,40] as these measures are more comparable to measures of adiposity in childhood. However, although infant BMI is commonly used to assess body mass in infant populations, other measures could be better predictors of true adiposity status as BMI is influenced by water, muscle, and fat [41]. Therefore, all measures were used for the assessment of growth and adiposity status as primary outcomes including FM, FFM, percent body fat, weight-for-age z-score, length-for-age z-score, and BMI-for-age z-score.

Ethics

Institutional Review Board at MetroHealth Medical Center approved all study procedures and each participant signed a written IRB-approved consent.

Statistical analysis

Analyses were conducted in STATA (version 14.2, Stata Corp.) and R (version 3.5.0, R Project) with an α of <0.05 indicating 2-tailed statistical significance. We examined what factors predicted infant size at birth in our study population. Linear regression was used to examine if infant sex, estimated gestational age at birth, or prepregnancy BMI were associated with infant outcomes at birth. These analyses were conducted both adjusting and not adjusting for GDM status to examine the effect of GDM exposure.

LCMM

To evaluate patterns of body composition growth across infancy and differences between analytic approaches, we applied LCMM. The LCMM package in R was used to estimate latent class mixed models in a maximum likelihood framework. Although robust for examining time-varying factors concerning growth and body composition parameters, longitudinal regression models may not fully capture the nuanced growth patterns that infants experience [42]. Through LCMM, classes, or subgroups, are identified based on similar growth patterns between participants allowing for the assumption that growth trajectories are not parallel [43,44].

LCMM is a data-driven approach to identify similar patterns of change in longitudinal data. To determine the appropriate number of groups, in LCMM, one must fit iterations of the data using model fit criteria. For this analysis, we fit and examined 2–4 classes for each primary outcome, accounting for age and the shape of the curves. More than 4 classes were unable to be used due to our smaller sample size and LCMM was not able to identify 5 or more unique classes. To do this, we fit models with and without splines and with varying transformations of age including age alone and age-squared terms. They were used in the final model if they improved the Bayesian Information Criterion. Our selected models had the following terms: fat mass, FFM, and weight-for-age z-score had splines, age, and age squared, BMI z-scores had splines and age, percent body fat had age, and length-for-age z-scores had splines. LCMM assigned infants into the classes for which they had the highest probability of belonging in for each model separately. Then, the most optimal model was chosen by assessing the shape of the curve and minimizing Bayesian Information Criterion and maximum likelihood while maintaining $\geq$10% of the sample in each class to support subsequent analyses (goodness-of-fit criteria for each model presented in Supplemental Table 1).

After selecting the most suitable LCMM models, multinomial logistic regression was used to determine predictors of trajectory class membership in STATA. Covariates were included independently to examine their relationship with the dependent variable. Those that improved model fit using Bayesian Information Criterion were included in the final regression model. The trajectory class with the most optimal growth (e.g., lowest FM gain) was used as the reference group in each model. GDM exposure status was used as the primary exposure in the models. Covariates used in the models included maternal height, total gestational weight gain, education status, estimated infant gestational age, and size for gestational age at birth. Smoking status, race, and maternal BMI were included in the original model analysis but did not improve model fit, were not significant for any class for any model, and did not influence coefficients of the other covariates by 10% and therefore were not used. In the percent fat LCMM trajectory group, a chi-square analysis was performed to test for differences between groups by infant sex. Chi-square analyses were also performed to test for differences between LCMM groups and GDM exposure for all models.

Results

A total of 198 infants (104 GDM exposed and 94 GDM unexposed) were included in analyses and followed for an average of 383 d (Supplemental Figure 1). All infants had a birth visit, 68 had 2 total visits (51% GDM exposed), 45 had 3 total visits (51% GDM exposed), and 85 had 4 total visits (54% GDM exposed). Infant characteristics at birth comparing female and male infants stratified by GDM exposure are reported in Supplemental Table 2 with female infants exposed to GDM in utero weighing more, having higher FFM, and a higher FFM index compared with males.

As shown in Table 1, a majority of the females enrolled in the study identified as non-Hispanic White. A larger number of females without GDM had some college or higher as their education compared with than those not diagnosed with GDM. Infant size for gestational age classification varied by GDM exposure with a larger number of infants exposed to GDM being LGA and a smaller number of infants exposed to GDM being small for gestational age.

Predictive models of infants' size at birth, unadjusted and adjusted for GDM status, show that after adjustment for GDM, associations between prepregnancy BMI and infant birthweight were attenuated (Table 2). Longer gestational age predicted greater percentage body fat

TABLE 1
Characteristics of mothers and infants included in the analytic sample.

	All (n = 198)	GDM+ (n = 104)	GDM− (n = 94)
Mother			
Age (y)	29.9 ± 0.4[1]	30.1 ± 0.6	29.7 ± 0.5
Primiparous, yes	60 (30.3)[2]	26 (25)	34 (36.2)
Race, identify as White	158 (79.8)	73 (70.2)	85 (90.4)
Smoke cigarettes during pregnancy, yes	35 (17.7)	26 (25)	9 (9.6)
Education, some college or higher	105 (53.3)	37 (35.9)	68 (72.3)
Height (cm)	164.4 ± 0.5	163 ± 0.7	166 ± 0.7
Prepregnancy BMI (kg/m^2)	27.1 ± 0.5	30 ± 0.8	23.9 ± 0.5
BMI category, obesity	59 (30)	51 (49)	8 (8.5)
Gestational weight gain (lbs)	14.1 ± 0.5	13.8 ± 0.7	14.3 ± 0.5
Vaginal delivery	140 (70.7)	68 (65.4)	72 (76.6)
Infant			
Male sex	96 (48.5)	47 (45.2)	49 (52.1)
Estimated gestational age (wk)	38.8 ± 0.1	38.5 ± 0.13	39.2 ± 0.12
Size for gestational age			
Large	31 (15.75)	23 (74.2)	8 (25.8)
Average	156 (78.8)	78 (50)	78 (50)
Small	11 (5.6)	3 (27)	8 (73)
Weight at birth (kg)	3.3 ± 0.49	3.4 ± 0.49	3.3 ± 0.48
Fat mass at birth (kg)	0.38 ± 0.2	0.43 ± 0.2	0.33 ± 0.19
Fat-free mass at birth (kg)	2.9 ± 0.4	2.9 ± 0.37	2.9 ± 0.35
Body fat at birth (%)	11.1 ± 4.8	12.4 ± 4.5	9.6 ± 4.6
BMI at birth (kg/m^2)	13.2 ± 1.36	13.5 ± 1.37	12.9 ± 1.3

Abbreviations: GDM+, gestational diabetes mellitus positive; GDM −, gestational diabetes mellitus negative.
[1] Mean ± SD (all such values).
[2] *n* (%) (all such values).

TABLE 2
Predictors of infant anthropometric and body composition measures at birth, adjusted and unadjusted for gestational diabetes mellitus[1].

	Length (cm) β (95% CI)	Weight (kg) β (95% CI)	Fat mass (kg) β (95% CI)	Fat-free mass (kg) β (95% CI)	Percent body fat β (95% CI)
Without GDM adjustment					
Infant sex, female	0.95[3] (0.4, 1.5)	0.17[2] (0.04, 0.3)	−0.01 (−0.06, 0.04)	0.18[3] (0.08, 0.3)	−0.87 (−2.2, 0.4)
Estimated gestational age (wk)	0.59[3] (0.4, 0.8)	0.13[3] (0.08, 0.2)	0.03[2] (0.007, 0.05)	0.10[3] (0.06, 0.1)	0.44 (−0.05, 0.9)
Prepregnancy BMI	0.009 (−0.03, 0.04)	0.01[2] (0.002, 0.2)	0.007[3] (0.004, 0.01)	0.003 (−0.003, 0.001)	0.18[3] (0.09, 0.3)
With GDM adjustment					
Infant sex, female	0.96[3] (0.4, 1.5)	0.16[2] (0.04, 0.3)	−0.01 (−0.07, 0.04)	0.18[3] (0.09, 0.3)	−0.96 (−2.2, 0.3)
Estimated gestational age (wk)	0.58[3] (0.4, 0.8)	0.13[3] (0.08, 0.2)	0.03[2] (0.01, 0.05)	0.10[3] (0.06, 0.1)	0.61[2] (0.12, 1.1)
Prepregnancy BMI	0.013 (−0.03, 0.05)	0.008 (−0.009, 0.02)	0.005[2] (0.001, 0.009)	0.003 (−0.004, 0.01)	0.12[2] (0.03, 0.2)
GDM exposure status	−0.17 (−0.7, 0.4)	0.10 (−0.04, 0.2)	0.09[2] (0.03, 0.1)	0.013 (−0.09, 0.1)	2.5[3] (1.1, 3.9)

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus.
[1] Top section of the table shows effects of covariate variables on anthropometric values at birth using linear regression that are unadjusted for GDM status, whereas the bottom section is adjusted for GDM status.
[2] $P < 0.05$.
[3] $P < 0.001$.

as did maternal prepregnancy BMI. Unadjusted plots stratified by GDM exposure indicate that infants exposed to GDM had a slower plot growth for FM (Figure 1D) and percent body fat gain (Figure 1F) beginning around 100 d of life compared with unexposed infants, whereas FFM appears similar the entire year (Figure 1E). Differences by exposure persisted at age 300–400 d for all indices except BMI and percent body fat. Comparisons of unadjusted anthropometric parameters and the number of participants at each visit are shown in Supplemental Table 3.

LCMM

Three latent growth trajectory classes from birth to 12 mo were identified for all growth and body composition parameters except weight-for-age z-score which had 4 latent growth trajectory class patterns identified (Figures 2 and 3; larger images of the trajectories are shown as Supplemental Figures 2–7). These trajectory curves show divergent patterns of growth, fat, and FFM at birth and across the first year. Some of the curves show differences (or similarities) in initial sizes at birth and subsequent patterns of change thereafter, as noted by the varying slopes of the curves. Average baseline and 1-y body composition values for all trajectory classes are shown in Supplemental Table 4. For example, for FM (model 1), class 1 started off with the highest FM and ended with the highest FM, whereas classes 2 and 3 started around the same FM and then diverged by 1 y, with class 3 ending up with higher FM at this point.

Chi-square analysis showed statistical differences in trajectory class membership by GDM exposure status for FM, percent body fat, and BMI z-score, but not for FFM, weight-, and length-for-age WHO z-score (Table 3).

Exposure to GDM in utero was associated with trajectory class membership for FM and percent body fat but this was not seen for FFM (Figure 2). Interestingly, GDM-exposed infants were 69% less likely to be in the largest FM trajectory class 1—with higher initial FM and rapid FM gain across infancy—and 73% less likely to be in the second largest FM class 3 compared with the smallest class 2 that was used as the reference and had the lowest FM trajectory. The proportion of males and females in each class was equally balanced for the FM model. The percent body fat model follows a similar pattern to the FM model; all 3 trajectory classes start somewhat similarly at birth (with class1 just slightly higher than classes 2 and 3) and show rapid acceleration from birth to 4 mo. All then, each follows a unique trajectory pattern from 4 mo onward as adipose tissue deposition is tempered. GDM exposure was associated with an 80% and 87% decrease in likelihood of infants belonging in percent body fat trajectory class 1 and class 3, respectively, compared with the smaller class 2.

The proportion of infants in the percentage body fat trajectories was similar by sex for class 2 (50% male/50% female), whereas class 1 had more males (56%) compared with females (44%), and class 3 had more females (60% female, 40% male). However, there was no significant difference between LCMM group and infant sex when a chi-square test was performed X^2 (df = 2, n = 198) = 3.7, P = 0.16 (data not shown).

Exposure to GDM in utero was associated with trajectory class membership for weight-for-age z-score and BMI-for-age z-score but not length-for-age z-score (Figure 3). For weight-for-age, GDM exposure was associated with an over 6-fold increase in the likelihood of belonging in class 3 (decrease in z-score from +1 to −0.5 over the first 100 d of life) compared with class 2 (steady increase from 0 to +1 over the first year of life). Exposure to GDM in utero was also associated with trajectory class membership for BMI-for-age z-scores. GDM exposed infants were 57% less likely to be in class 2 (increase in z-score from 0 to almost +2 over the first year) compared with class 3 (remained steady at −1).

Discussion

In this cohort, infants exposed to GDM in utero had higher mean FM, BMI, and percentage body fat at birth but lower mean FM and percent body fat gain over the first year of life with no differences in FFM at birth or across the first year. Interestingly, infants exposed to GDM in utero had greater adiposity at birth but our latent class trajectory analysis showed their growth patterns were more likely to slowly gain body fat over the first year of life compared with infants who were unexposed to GDM.

Not all infants grow exactly as these LCMM patterns showed but these are identifiable trends. For example, using LCMM, we saw that infants exposed to GDM were more likely to be in the groups with lower mean FM accrual across the first year of life. Growth trajectory curves that follow this downward trend in growth percentiles have been termed catch-down growth in previous literature [21]. Heavier infants at birth often demonstrate catch-down growth, meaning that although they have a gradual net gain in weight, their growth rate may actually be lagging compared with babies with lower birthweight based on growth weight percentiles. Overall, for our cohort, infants exposed to

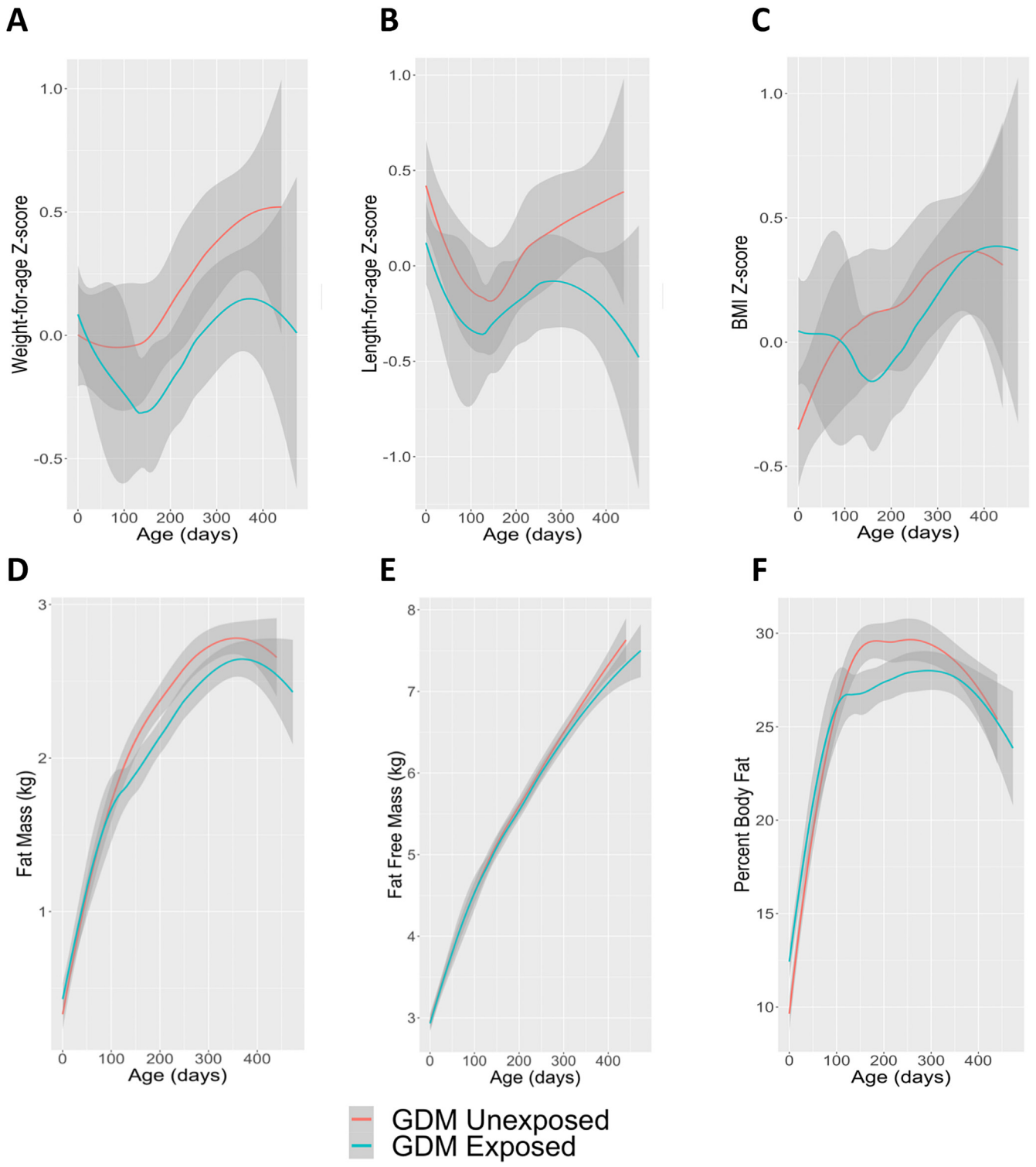

FIGURE 1. Unadjusted growth plots of infants exposed and unexposed to GDM in utero included in the analytic sample from birth to 12 mo of age. Growth plots are shown for all growth and body composition measurements used for latent class mixture modeling growth analysis. The y-axes differ by measurement as they depend on the anthropometric or z-score values. The line indicates the mean value for the group and the shaded areas around the line are the confidence intervals. GDM, gestational diabetes mellitus.

GDM in utero were more likely to experience growth patterns for FM and percent body fat using LCMM that indicate catch-down growth.

Similar to our cohort, in Brazil, infants exposed to GDM experienced catch-down growth for weight in the first 12 mo of life and this was persistent until 24 mo of age [45]. In a Chinese birth cohort from a similar time period to our study (1997), GDM exposure in utero was associated with a lower BMI z-score in infancy but higher BMI z-scores during childhood and adolescence [46]. Others have shown that BMI growth is slow during the first 6 mo of life for infants exposed to GDM (even when BMIs do not differ at birth by GDM exposure) but

Model 1: Relative Risk Ratio (95% CI) of Fat Mass Trajectory Class Membership

	Class 1 (n=31, 48% exposed)	Class 2 (n=64, 67% exposed)	Class 3 (n=103, 45% exposed)
GDM Exposed	0.31 (0.11, 0.82)	Reference	0.27 (0.13, 0.57)
Infant Sex (female)	1.34 (0.56, 3.3)	Reference	1.26 (0.65, 2.4)
Gestational Weight Gain (lbs.)	1.01 (0.5, 1.1)	Reference	0.98 (0.93, 1.03)
Maternal Education (≥ high school degree)	0.38 (0.15, 1.01)	Reference	0.48 (0.23, 0.99)

Model 2: Relative Risk Ratio (95% CI) of Fat Free Mass Trajectory Class Membership

	Class 1 (n=68, 49% exposed)	Class 2 (n=53, 79% exposed)	Class 3 (n=77, 38% exposed)
GDM Exposed	Reference	1.13 (0.5, 2.4)	0.73 (0.3, 1.6)
Infant Sex (female)	Reference	0.32 (0.15, 0.7)	0.11 (0.05, 0.25)
Maternal Height (cm)	Reference	0.97 (0.9, 1.02)	0.93 (0.88, 0.98)
Estimated Gestational Age (weeks)	Reference	0.93 (0.7, 1.2)	0.65 (0.5, 0.9)

Model 3: Relative Risk Ratio (95% CI) of Percent Body Fat Trajectory Class Membership

	Class 1 (n=68, 49% exposed)	Class 2 (n=53, 79% exposed)	Class 3 (n=77, 38% exposed)
GDM Exposed	0.20 (0.08, 0.5)	Reference	0.13 (0.05, 0.3)
Infant Sex (female)	0.89 (0.4, 1.9)	Reference	2.1 (0.94, 4.6)
Gestational Weight Gain (lbs.)	0.96 (0.9, 1.02)	Reference	0.93 (0.88, 0.99)
Estimated Gestational Age (weeks)	1.2 (0.89, 1.6)	Reference	0.83 (0.61, 1.1)

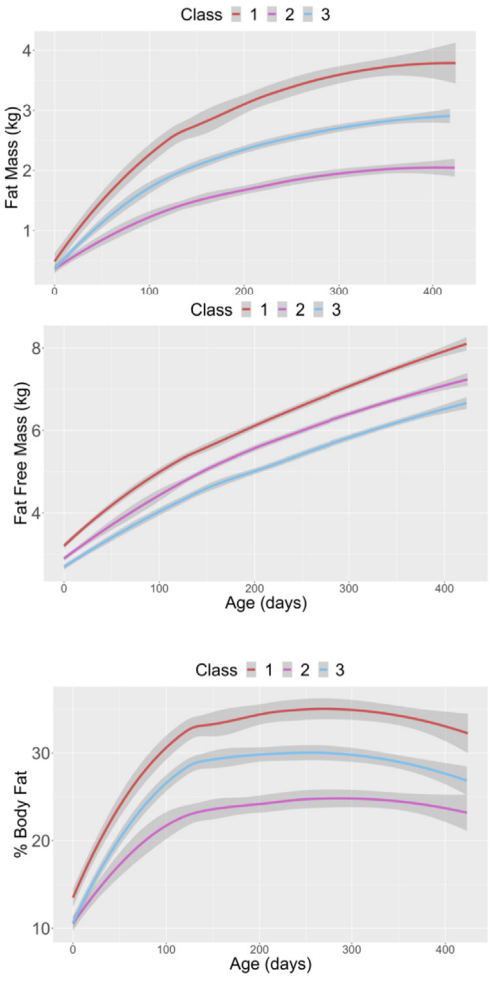

FIGURE 2. Three-class latent class mixed models with one 4-class latent class mixed model and corresponding multinomial logistic regression estimates showing relative risk ratio (95% confidence interval) for likelihood of being in each class relative to the reference class. Subgroups experience distinct trends in growth patterns over time for each of the anthropometric measures. The line indicates the mean growth trajectory for the group and the shaded areas around the line are the confidence intervals.

after 6-mo BMI growth in GDM is accelerated compared with infants unexposed to GDM up until the age of 5 [47]. Also similar to our findings, it has been seen that infants exposed to GDM experience catch-down growth for FM at 6 mo of age [48]. However, to our knowledge, our study is the first to show growth and body composition trajectories of catch-down growth using LCMM up to infant age 12 mo.

The Maternal-Fetal Medicine Units follow-up study of participants treated for mild GDM showed that although there were neonatal benefits of treating mild GDM at follow-up at age 5–10, there was no difference in the reduction of childhood obesity [49]. Similarly, in the Hyperglycemia and Adverse Pregnancy Outcome follow-up study in females with GDM, in the fully adjusted model 4 (maternal BMI at 28–32 wk gestation) the association of overweight/obesity was no longer significant [50]. Further in the same follow-up study, adjusting for maternal BMI attenuated the association of GDM with childhood measures of adiposity measured using air plethysmography (Pea Pod), although other associations of maternal GDM and childhood adiposity remained significant [50].

Assessing infant FM and relative adiposity (i.e., FM index or percentage body fat) is a clinically relevant area of research as these measures can be a predictor of childhood health outcomes. High-risk infants, such as those exposed to GDM in utero, may need additional growth monitoring as they can be more prone to adverse health outcomes later in life. Overall, in our sample, we saw differences in BMI and percent body fat between infants exposed and unexposed to GDM in utero which did not persist at 1 y of age as seen in Figure 1. This indicates the need to study further the long-term risk of obesity and accrual of FM in those exposed to GDM in utero in childhood and beyond.

One possible explanation for the elevated infant adiposity at birth we saw in our study in infants exposed to GDM is a hyperglycemic environment in utero. A hyperglycemic uterine environment could lead to altered fetal gene expression that affects metabolism [51]. It has previously been seen that blood glucose levels of pregnant females were associated with levels of leptin in the cord blood of the infant at birth which could influence infant growth trajectories, behavior, and adiposity later in life [52–54]. Other contributors to excess adiposity at birth [55] and into childhood [56] include maternal prepregnancy overweight or obesity and excess gestational weight gain, which are common among those with GDM and collectively are associated with an increased risk for excess FM at birth [57,58].

Maternal hyperglycemia is also known to induce fetal hyperinsulinemia which leads to not only increased fetal weight gain but also increased size of insulin-sensitive organs such as the heart, specifically septal hypertrophy [59] and other insulin-sensitive tissues [60]. Exposure to GDM in utero is known to affect cardiac health into childhood

Model 4: Relative Risk Ratio (95% CI) of Weight-for-Age Z-score Trajectory Class Membership

	Class 1 (n=58, 52% exposed)	Class 2 (n=50, 42% exposed)	Class 3 (n=35, 71% exposed)	Class 4 (n=55, 51% exposed)
GDM Exposed	2.4 (0.9, 5.8)	Reference	6.2 (2.1, 18)	1.6 (0.6, 3.8)
Maternal Education (≥ High School Degree)	1.1 (0.4, 2.5)	Reference	2.4 (0.9, 6.5)	1.6 (0.7, 3.9)
Gestational Weight Gain (lbs.)	1.1 (1.0, 1.2)	Reference	1.1 (1.03, 1.2)	1.0 (0.9, 1.1)
Estimated Gestational Age (weeks)	1.6 (1.2, 2.3)	Reference	1.2 (0.8, 1.7)	0.80 (0.6, 1.1)

Model 5: Relative Risk Ratio (95% CI) of Length-for-Age Z-score Trajectory Class Membership

	Class 1 (n=71, 46% exposed)	Class 2 (n=71, 56% exposed)	Class 3 (n=56, 55% exposed)
GDM Exposed	Reference	1.08 (0.5, 2.3)	0.53 (0.2, 1.3)
Maternal Height (cm)	Reference	0.94 (0.89, 0.98)	0.92 (0.87, 0.97)
Maternal Education (≥ High School Degree)	Reference	0.90 (0.42, 1.9)	0.38 (0.16, 0.88)
Gestational Weight Gain (lbs.)	Reference	1.01 (0.96, 1.07)	0.96 (0.9, 1.02)
Estimated Gestational Age (weeks)	Reference	0.84 (0.63, 1.1)	0.54 (0.4, 0.75)

Model 6: Relative Risk Ratio (95% CI) of Body Mass Index Z-Score Trajectory Class Membership

	Class 1 (n=49, 63% exposed)	Class 2 (n=50, 38% exposed)	Class 3 (n=99, 55% exposed)
GDM Exposed	1.3 (0.58, 2.9)	0.43 (0.19, 0.94)	Reference
Maternal Education (≥ high school degree)	0.33 (0.15, 0.73)	0.54 (0.25, 1.16)	Reference
Gestational Weight Gain (lbs.)	1.02 (0.97, 1.1)	0.99 (0.94, 1.04)	Reference
Estimated Gestational Age (weeks)	1.5 (1.1, 2.0)	1.05 (0.8, 1.4)	Reference

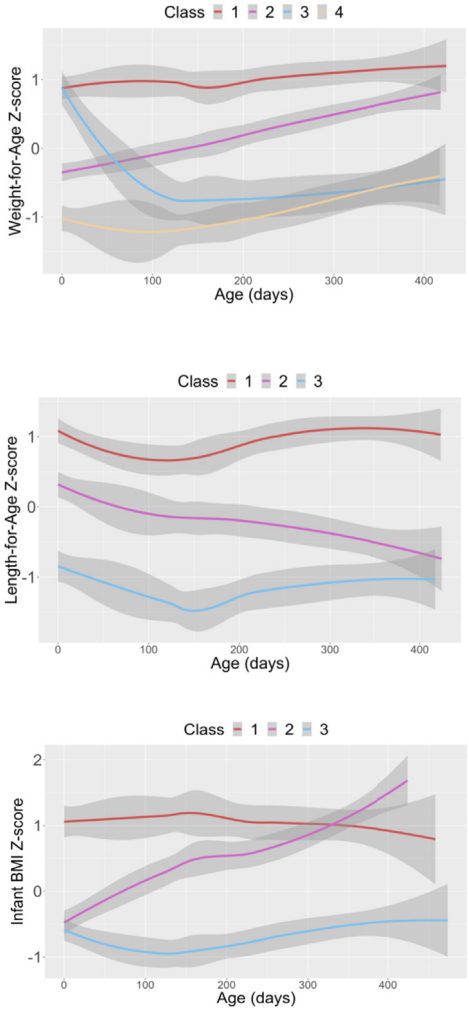

FIGURE 3. Three-class latent class mixed models and corresponding multinomial logistic regression estimates showing relative risk ratio (95% confidence interval) for likelihood of being in each class relative to the reference class. Subgroups experience distinct trends in growth patterns over time for each of the anthropometric measures. The line indicates the mean growth trajectory for the group and the shaded areas around the line are the confidence intervals.

TABLE 3
Body composition and growth trajectory class trajectory by GDM exposure status ($n = 198$).

	GDM exposure (%)				Chi-square
	Class I	Class II	Class III	Class IV	
FM	48	67	45		8.3, $P = 0.016$
FFM	49	79	38		0.19, $P = 0.91$
Percent body fat	49	79	38		22.4, $P < 0.001$
WAZ	52	42	71	51	7.31, $P = 0.06$
LAZ	46	56	55		1.63, $P = 0.44$
BMIZ	63	38	55		6.6, $P = 0.036$

Abbreviations: BMIZ, BMI z-score; FM, fat mass; FFM, fat-free mass; GDM, gestational diabetes mellitus; LAZ, length-for-age z-score; WAZ, weight-for-age z-score.

and adolescence; 1 study found that girls exposed to GDM (spanning ages 10–17 y of life) had elevated total cholesterol and LDL cholesterol, whereas boys exposed to GDM had elevated blood pressure [61]. However, these associations between GDM exposure and increased cardiac adverse outcomes may be impacted when the pregnant person's blood glucose is tightly controlled throughout pregnancy [15].

One of the strengths of this study was the use of advanced modeling techniques, LCMM, to examine nuanced trajectories of growth and body composition across the first year of life. Using LCMM to examine growth patterns of infants exposed and unexposed to GDM allowed us to identify subgroup growth patterns and features that are naturally occurring in our study population and may be challenging to ascertain with analytic techniques that pool divergent groups together or focus on cross-sectional differences. This approach allows us to determine if there are underlying commonalities in growth trends and if GDM is associated with a certain underlying growth trend.

Although there are many strengths to this study, including longitudinal assessment of body composition and TOBEC, there are weaknesses. One weakness is the lack of dietary information of infants during the first year of life. We were unable to use breastfeeding as a covariate in the analyses which is known to affect infant growth and adiposity [62,63]. We were also missing information on timing of solid introduction and types of foods (such as foods known to increase adiposity like sugar-sweetened beverages [64]) as these have been

shown in the past to affect subsequent BMI in toddlerhood and childhood and could have influenced the diverging growth trajectories after 100 d of life we saw in the unadjusted growth plots for FM and percent body fat gain [65]. We also recognize that the smaller sample size, sample differences in characteristics compared with the general United States population, asymmetric recruitment distribution, and older age of the data are limitations.

We also do not know reported specifications of the pregnant persons medical or obstetric complications. When assessing size for gestational age, 5 values had to be estimated using clinical judgment as they were coded as missing in the original set of data from the hospital which had categorized the other infants using their hospital protocol. Prenatal glucose values were not collected and thus were unable to quantify the uterine milieu which, as stated above, is known to affect fetal growth and development [66].

The findings from this study indicate that further research in this area is needed to support females with GDM during pregnancy to better understand and improve both short- and long-term health for infants exposed to GDM in utero. Long-term effects of the infant growth trajectories seen in this study should be studied, especially those related to catch-down growth. It has been seen that a euglycemic uterine environment can help mitigate adverse infant outcomes at birth and possibly further into life [67]. Infants that experienced these slower growth trajectories could possibly benefit from interventions during toddlerhood and childhood to mitigate the increase in adiposity and BMI seen in previous literature in similar samples.

In conclusion, infants exposed to GDM in utero in our sample experienced higher weight and adiposity at birth when compared with infants unexposed but there was no difference in FFM. LCMM is useful for modeling longitudinal growth in high-risk and specialized populations that experience growth patterns different from infants with no adverse exposures or health risks. Using LCMM, across the first year of life infants exposed to GDM experienced a slower growth trajectory for FM and percent body fat but not FFM. These catch-down growth trajectories seen in our sample challenge the idea that GDM exposure in utero is detrimental to obesity beyond infancy and indicate the need for further investigation.

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Author contributions

The authors' responsibilities were as follows – PC: had oversight over data collection; PC, RRR, EMW: conceptualized this analysis; RRR: conducted data cleaning and analysis; EMW, CEL, PC, ARN: contributed to the analysis planning and development; and all authors: interpreted the data, contributed to the manuscript during drafting and editing, and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.10.020.

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