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The Impact of *In Utero* Exposure to Diabetes on Childhood Body Mass Index Growth Trajectories: The EPOCH Study

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Abstract

Objective—To examine associations between exposure to maternal diabetes *in utero* and body mass index (BMI) growth trajectories from birth through 13 years of age among a diverse cohort of youth.

Study design—Mixed linear effects models were constructed to assess differences in BMI and BMI growth velocity from birth through 13 years of age for 95 subjects exposed to diabetes *in utero* and 409 unexposed subjects enrolled in a retrospective cohort study.

Results—The overall BMI growth trajectory (adjusted for sex and race/ethnicity) was not significantly different for exposed and unexposed subjects from birth through 26 months of age (p=0.48). However, the overall growth trajectory from 27 months of age through 13 years differed by exposure status (p=0.008), adjusted for sex and race/ethnicity. The difference was primarily due to a significantly higher BMI growth velocity among exposed youth between 10–13 years, increasing by 4.56 kg/m^2 compared to 3.51 kg/m^2 in the unexposed (p=0.005). Control for demographic variables, socioeconomic factors and maternal pre-pregnancy BMI did not alter the observed associations.

Conclusions—Exposure to maternal diabetes *in utero* accelerates BMI growth in late childhood thus increasing long-term obesity risk.

Keywords

Gestational diabetes; fetal overnutrition; fetal exposure to diabetes; childhood obesity; childhood BMI; growth trajectory

The rapid increases in childhood obesity observed worldwide herald an alarming forecast for future burden of hypertension, diabetes and cardiovascular disease (1–3). Significant research has suggested the existence of critical periods for the development of childhood obesity. Fetal life, the time period of greatest developmental plasticity, has been suggested to be one such important period (4). Indeed, several pregnancy factors have been associated with greater obesity in the offspring, including maternal pre-pregnancy BMI (5,6), gestational weight gain (7,8), and gestational diabetes (9–12).

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The possibility that intrauterine exposure to maternal diabetes could place offspring at increased risk for obesity and related metabolic consequences later in life has generated considerable interest. Maternal diabetes is a recognized risk factor for excess fetal growth, macrosomia and increased fetal adiposity (13,14). However, less is known about the pattern of postnatal growth in offspring exposed to maternal diabetes. In unexposed children, body mass index (BMI) increases rapidly during the first 9–12 months of life, then declines reaching a minimum at 4 to 6 years of age before beginning a gradual increase throughout adolescence and most of adulthood (15). Cross-sectional analyses have suggested that Pima Indian offspring exposed to diabetes *in utero* experience a period of catch-down growth between one to two years of age followed by higher BMI throughout childhood and adolescence compared to unexposed Pima youth (16–18). However, the extent and pattern of the influence of *in utero* diabetes exposure on the childhood BMI trajectory is unknown. The study of entire growth trajectories, rather than cross-sectional analyses across specific time points, allows for a better understanding of how and when fetal exposures influence postnatal growth through childhood as a whole, and therefore may generate information about optimal time periods for focused preventative interventions.

To address this, our study explored BMI growth trajectories from birth through 13 years of age among a diverse cohort of children exposed and unexposed to maternal diabetes in pregnancy, adjusting for the effects of potential confounders.

METHODS

This report uses data from a retrospective cohort study conducted in Colorado: Exploring Perinatal Outcomes among Children (EPOCH). Participants were 6–13 year old offspring of singleton pregnancies, born at a single hospital in Denver between 1992 and 2002, whose biological mothers were members of the Kaiser Permanente of Colorado Health Plan (KPCO), and who were still KPCO members and living in Colorado over the study period (2006–2009).

For this analysis, eligible participants were children exposed to diabetes *in utero* (exposed group) and a random sample of children not exposed to diabetes *in utero* without intrauterine growth restriction, defined as birth weight for gestational age score < the 10^{th} percentile (unexposed group). The study was approved both by the Colorado Multiple Institutional Review Board and Human Participant Protection Program. All participants provided written informed consent and youth provided written assent.

Exposure definition

Physician-diagnosed maternal diabetes status was ascertained from the KPCO Perinatal database, an electronic database linking the neonatal and perinatal medical record. The database contains data that define delivery events for each woman. Gestational diabetes (GDM) is coded as present if diagnosed through the standard KPCO screening protocol (described below) and absent if screening was negative. Since the 1990s, KPCO has routinely screened for GDM in all non-diabetic pregnancies using a two-step standard protocol. At 24–28 weeks, all pregnant women are offered screening with a 1-h 50-g oral glucose tolerance test (OGTT). Patients with blood glucose value ≥140 mg/dl undergo a diagnostic 3-hour 100-g diagnostic OGTT. GDM is diagnosed when two or more glucose values during the diagnostic OGTT meet or exceed the criteria for a positive test, as recommended by the National Diabetes Data Group (19). The KPCO screening and diagnostic protocols have remained constant over time. Exposure to diabetes *in utero* was defined as presence of pre-existent diabetes or GDM diagnosed during the index pregnancy. In addition, birth weight, birth length, gestational age, and maternal pre-pregnancy weight were obtained from the database.

Childhood height and weight measurements

All participants were invited to a research office visit in which standard anthropometric measures were recorded. Current height and weight were measured in light clothing and without shoes. Weight was measured to the nearest 0.1 kg using a portable electronic SECA scale. Height was measured to the nearest 0.1 cm using a portable SECA stadiometer with a fine-gauge knitting needle. Height and weight were measured and recorded twice, and an average was taken. Scales and stadiometers were calibrated every two months using standard weights for scales, and aluminum measuring rod for the stadiometer. Previously recorded measures of recumbent length (up to age 2 years), standing height (after the child is able to stand) and weight from pediatric office visits were abstracted from the KPCO medical record. For children with an enrollment gap, medical records from non-KPCO providers were obtained. Weight and height measurements at provider offices were obtained with similar instruments over time but were taken under less standardized conditions than in a research setting. The median number of BMI measurements for subjects was 10 (ranging from 1 to 35). BMI was calculated as kg/m^2.

Other measurements

Race/ethnicity was self-reported using 2000 U.S. Census-based questions and categorized as Hispanic (any race), non-Hispanic white (NHW), or non-Hispanic African-American (AA). Maternal pre-pregnancy body mass index (BMI, kg/m^2) was calculated from the KPCO measured weight before the last menstrual cycle preceding pregnancy and height collected at the in-person research visit. Maternal level of education and total household income at the time of birth were self-reported during the research office visit. Pubertal development at the time of the EPOCH visit was assessed by child-self report with a diagrammatic representation of Tanner staging adapted from Marshall and Tanner (20) and youth were categorized as Tanner < 2 (pre-pubertal) and ≥ 2 (pubertal).

Statistical Analysis

Mixed effects linear models were constructed to assess differences in average BMI and BMI growth velocity for subjects exposed and unexposed to DM *in utero*. This modeling approach allows for intrasubject correlation of repeated measures on subjects and accounts for an unbalanced design in the number of BMI observations on each subject and the age (time) at which they were collected. Due to the change in use of recumbent length to standing height around the age of 2 years, two separate growth curves were developed to model the BMI trajectory over time. The first model was fit for the infancy period from birth through 26 months and a second model for the childhood period from 27 months to 13 years. An iterative process was used to determine the degree of polynomial in age for both its random and fixed effects. Two, three, and four degree polynomial functions were explored by adding linear, quadratic, and cubic terms. Both final models used a quadratic polynomial for the fixed effects of age on BMI and linear random effect. A spline with a single knot at 11 months was included in the infancy period model (from birth through 26 months) which allowed a quadratic function before and after the knot. The best fit was determined based on each model's ability to predict BMI at specific ages (6 months, 1 year, 2 years, etc.) compared to a categorical linear effects model.

The BMI growth model for the infancy period (birth-26 months) for the *i*th subject at time *j* (i.e., age in months) took the form:

$$
\begin{aligned}
y_{ij} = {} & B_0 + B_1 age_{ij} \\
& + B_2 age_{ij}^2 \\
& + B_3 exposure_i \\
& + B_3 age_{ij} * exposure_i \\
& + B_4 age_{ij}^2 * exposure_i \\
& + B_5 (age_{ij} \\
& - 11) * [I_{age(ij)>11month}] + B_6 (age_{ij} - 11)^2 * [I_{age(ij)>11month}] + B_7 (age_{ij} - 11) * [I_{age(ij)>11month}] * exposure_i \\
& + B_8 (age_{ij} - 11)^2 * [I_{age(ij)>11month}] * exposure_i \\
& + b_{0i} + b_{1i} * age_{ij} + e_{ij} + \text{covariates}
\end{aligned}
$$

The terms $b_{0i} + b_{1i}$ are the subject specific random intercept and random slope for the *i*th subject and $I_{age(ij)>11month}$ is an indicator variable for ages of 11 months and older. The BMI growth model for the childhood period (27 months – 13 years) took the form:

$$y_{ij} = B_0 + B_1 age_{ij} + B_2 age_{ij}^2 + B_3 exposure_i + B_3 age_{ij} * exposure_i + B_4 age_{ij}^2 * exposure_i + b_{0i} + b_{1i} age_{ij} + \text{covarites.}$$

Covariates for the base model included exposure to diabetes *in utero*, sex and race/ethnicity as fixed effects, and the fully adjusted model added gestational age, maternal age, maternal pre-pregnancy BMI, maternal education and household income at birth as fixed effects. The average BMI during the infancy and childhood periods, as well as BMI growth velocity during specific age ranges were estimated for exposed and unexposed subjects from the base model.

RESULTS

A total of 95 children exposed to diabetes *in utero* (87 offspring of GDM mothers and 8 of mothers with type 1 diabetes) and 409 unexposed youth participated in the EPOCH study and had complete data on variables of interest. The participants were 49.0% non-Hispanic white, 42.5% Hispanic and 8.5% African American. At the time of birth, 96.8% of the mothers had at least a high school education and 53.9% had a household income greater than $50,000/year. The average age of the child at study visit was 9.5±1.7 and 10.6±1.3 years for exposed and unexposed youth, respectively (p<.0001). Additionally, 30% of exposed subjects self-reported a Tanner stage ≥ 2 at the study visit, indicating they had begun puberty, compared to 50% of unexposed subjects (p=0.0005). Mothers of exposed offspring were, on average, older at delivery than those of unexposed offspring (33.1±5.2 vs. 30.0±5.4, p=0.03), and had a higher pre-pregnancy BMI (27.7±6.2 vs. 25.7±6.6, p=0.01).

Figure 1 shows the modeled BMI growth trajectories for the infancy period from birth through 26 months for youth exposed and unexposed to DM *in utero*. Over this age range, neither the average BMI from birth to 26 months (p=0.53), nor the BMI growth trajectories (p=0.48) were significantly different for exposed and unexposed youth. The BMI growth trajectory for the childhood period from 27 months to 13 years is presented in Figure 2. Exposed youth had significantly higher average BMI over this range (p=0.01) and an accelerated BMI growth trajectory (p=0.008) compared with unexposed youth.

Table I shows the BMI growth velocity of subjects exposed and unexposed to DM *in utero*, as well as the number of BMI data points available in each age-group period. Based on the quadratic spline model from birth through 26 months (adjusted for sex and race/ethnicity)

we estimate that, on average, offspring of diabetic pregnancies gained 2.19 kg/m^2 and unexposed offspring gained 2.70 kg/m^2 in the first 9 months of life, a difference of −0.51 kg/m^2 that was not statistically significantly (p=0.12). Between 9 and 12 months of age, the model reflected a decrease in BMI with exposed infants losing, on average, −0.05 kg/m^2 compared to a loss of −0.36 BMI in the unexposed (p=0.03). The negative BMI growth trajectory continued from 13–26 months with no significant differences by exposure. Based on the quadratric model for the older ages (adjusted for sex, race/ethnicity) we found that, on average, the growth trajectory decreased from 27 months through 3 years by −0.22 kg/m^2 and −0.02 kg/m^2 for exposed and unexposed youth, respectively (p=0.19). The BMI growth velocity increased from ages 4 years though 6 years, similarly for exposed and unexposed youth (0.35 kg/m^2 and 0.40 kg/m^2, respectively, p=0.73) and continued to accelerate from 7 through 9 years, increasing by 1.73 kg/m^2 and 1.44 kg/m^2 in exposed and unexposed, respectively, (p=0.13). Between 10–13 years, the BMI growth velocity was significantly higher among the exposed youth, increasing by 4.56 kg/m^2 compared to 3.51 kg/m^2 among the unexposed youth (p=0.005).

Table II presents the parameter estimates for the fixed effects of exposure to diabetes *in utero* from the fully adjusted model (Model 2) controlled for sex, race/ethnicity, gestational age, maternal age, maternal pre-pregnancy BMI, maternal education and household income at birth. From birth through 26 months of age, higher BMI was independently associated with male sex (p=0.0001), higher gestational age (p=0.004), higher pre-pregnancy BMI (<. 0001), higher household income (p=0.04), and older maternal age (p=0.02), but not with exposure to diabetes *in utero* (adjusted p=0.21). However, from 27 months to 13 years of age, exposure to diabetes *in utero* was associated with an average higher BMI (adjusted p=0.02) and an altered BMI growth trajectory (adjusted p=0.009) among the exposed, an effect that was not attenuated by controlling for demographic variables (sex, race/ethnicity) socioeconomic factors (maternal education, income, maternal age), or a surrogate marker of genetic predisposition to obesity (maternal pre-pregnancy BMI). Other factors associated with higher childhood BMI between 27 months of age and 13 years were male sex (p=0.02), and pre-pregnancy BMI (p=0.03).

DISCUSSION

In a multi-ethnic population from Colorado, we found that exposure to diabetes *in utero* was associated with an altered growth trajectory in children (27 months through 13 years of age, p=0.008), in particular a higher BMI growth velocity starting at ages 10 to 13 years (p=0.005). The effect of exposure on the BMI growth trajectory in childhood was independent of potential confounders such as demographic (sex, race/ethnicity) and developmental characteristics (gestational age), or markers of other *in utero* exposures (maternal age, income and education, pre-pregnant BMI). Importantly, no significant differences in growth trajectories were noted in infancy and early childhood. This study used longitudinal analysis to examine the impact of *in utero* diabetes exposure on BMI growth trajectories from birth to adolescence.

Our findings are consistent with the long-term patterns of accelerated BMI growth associated with *in utero* diabetes exposure reported in other studies. Silverman et al (21) observed a period of catch-down growth among a population of NHW and AA offspring of diabetic pregnancies compared to offspring of non-diabetic pregnancies in Chicago. The initial period of poor growth or catch-down weight in the first year of life was followed by a higher BMI in adolescence among offspring of diabetic mothers relative to non-exposed peers. Among Pima Indian youth, Touger et al (18) reported a change in weight z score between birth and 1.5 years of age of −0.56 vs. 0.12, (p<0.01) for exposed verses unexposed offspring suggesting early catch-down growth, but a higher weight z score at age 7.7 years

of 1.26 in exposed vs. 0.00 in unexposed children ($p<0.01$). In an earlier study, Dabelea et al (17) reported no differences in mean BMI among Pima Indian sib-pairs exposed and unexposed to diabetes *in utero* at ages 5–8 years, but significantly higher BMI levels in exposed siblings at ages 9–12 years, which persisted throughout adolescence into young adulthood. Our study did not identify specific periods of catch-down growth in exposed versus unexposed infants; the overall growth trajectory up to 26 months of age was not significantly different between the two groups. Interestingly, in a recent follow up study of a randomized clinical trial in Australia, treatment of mild GDM did not result in BMI differences in offspring at 4–5 years of age (22). All the data summarized above suggested that the long-term effects of GDM exposure on childhood obesity become apparent later during childhood (e.g., during puberty). Our findings are consistent with previous reports and provide novel and direct evidence that exposure to diabetes *in utero* results in accelerated BMI growth starting in late childhood.

The mechanisms underlying the accelerated BMI growth trajectory in childhood among offspring of diabetic pregnancies are the object of extensive research. Several mechanisms that are not mutually exclusive may explain this association. They include genetic predisposition and shared familial factors, as well as specific intrauterine effects (i.e., fuel-mediated teratogenesis, also known as fetal overnutition). For example, exposure to maternal diabetes *in utero* may modulate delivery of lipid substrates to the fetus, resulting in adipocyte dysregulation and fatty acid accumulation (23). More research is needed in this area because distinguishing between specific intrauterine mechanisms and general familial (genetic and nongenetic) factors is important for the development of randomized trials aimed at testing effective interventions.

In our study, differences in pubertal development between exposed and unexposed offspring did not explain differences in growth trajectories (data not shown), and exposed offspring were in fact less likely to have begun puberty by the time of the EPOCH visit. However, the role of pubertal development as a potential mediator or modifier of the long-term consequences of exposure to diabetes *in utero* on childhood adiposity patterns requires additional study and prospective follow up of this cohort.

We believe that our data have important public health implications. Efforts to intervene or treat obese adults have generally been unsuccessful, and thus, identifying mechanisms and critical periods that influence obesity risk in future generations represent an important opportunity to develop targeted prevention efforts to break the vicious cycle of obesity. Importantly, the Bogalusa Heart Study demonstrated that cardiovascular risk factors, including obesity, track from childhood into adulthood (24). Our data suggest that exposure to diabetes *in utero* results in accelerated BMI growth during late childhood years. Further follow up of this cohort is necessary to determine if the accelerated growth trajectory continues into teenage and early adult period. Because no differences in growth trajectories were observed early in life, the perinatal and early childhood periods may represent windows of opportunity for targeted efforts aimed at preventing the increased risk of obesity associated with *in utero* exposure, manifesting in late childhood/early pubertal years. Such preventive strategies among high risk children include promotion of breastfeeding, which has been associated with reduced risk of obesity in late adolescence and adulthood (25), encouragement of physical activity, and promotion of healthy foods, such as fruits, vegetables, whole-grain breads and cereals, low fat diary products and no sweetened drinks.

Our study has several limitations. We did not have sufficient data points on each subject to construct individual growth curves or accurately estimate whether exposure to diabetes *in utero* influences the age at adiposity rebound, another marker of increased risk for later-life obesity (26). Our study, like others (27) used maternal pre-pregnancy BMI as a proxy for

genetic predisposition. This is problematic because maternal obesity is a risk factor for the exposure considered in this study (27,28) and may represent over adjustment. However, in our population, adjustment for maternal pre-pregnant BMI did not eliminate the observed relationship between exposure to diabetes i*n utero* and increased growth trajectory during late childhood, suggesting that the observed association is not completely accounted for by genetic predisposition to obesity. We were unable to assess the impact of maternal hyperglycemia less severe than the cutoff for diagnosis of GDM. Offspring exposed to less extreme levels of hyperglycemia *in utero* were captured in our unexposed group, thus possibly biasing our results towards the null. The relatively young age of our cohort prevented assessment of accelerated growth after puberty, when differences are likely to be more pronounced (29,30): only 30% of exposed youth and 50% of unexposed youth reported a Tanner stage greater than 2, indicating they had begun puberty. Prospective follow up of this population is necessary to understand the impact of exposure to diabetes *in utero* on BMI trajectories during teen and early adult years.

Our study also has important strengths. First, the longitudinal analysis utilizing mixed linear effects models made efficient use of the data, allowing us to explore more than just linear changes in BMI between two time periods. Our methods represent a novel approach to assess the influence of *in utero* diabetes exposure on childhood growth. Additional strengths include the ethnically diverse cohort including NHW, Hispanic and AA youth and our validated exposure, assessed without concern for recall bias.

In summary, this study provides novel evidence of an altered childhood growth patterns for youth exposed to diabetes *in utero*. Among a diverse population of young children, exposure to diabetes *in utero* was associated with an overall higher growth trajectory in late childhood and accelerated BMI growth velocity starting at ages 10 to 13 years, relative to unexposed children. These results provide further support for the hypothesis that fetal exposure to a diabetic intrauterine environment influences childhood growth and obesity risk.

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Abbreviations

BMI	Body Mass Index
DM	diabetes mellitus
EPOCH	Exploring Perinatal Outcomes Among Children
T2D	type 2 Diabetes
KPCO	Kaiser Permanente of Colorado
GDM	gestational diabetic mothers
OGTT	oral glucose tolerance test
NHW	non Hispanic AA, African-American

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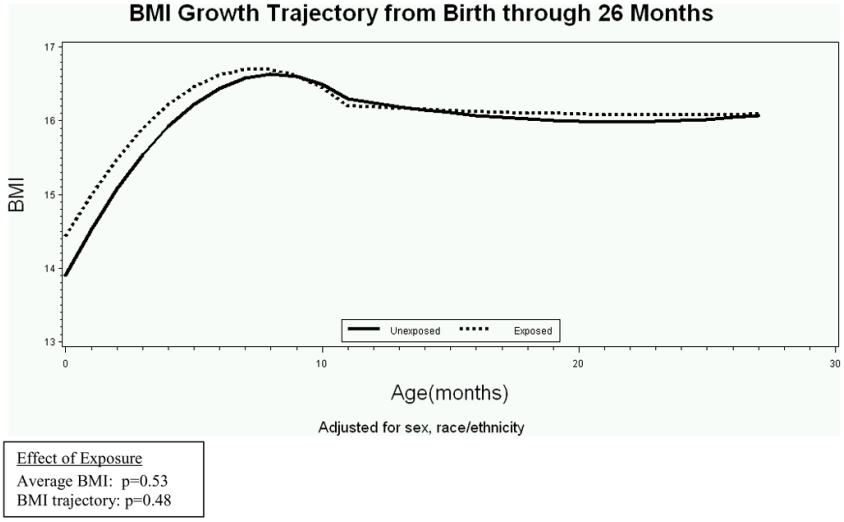

Figure 1.
Mean BMI curves for youth both exposed and unexposed to maternal diabetes *in utero* from birth - 26 months of age, adjusted for sex and race/ethnicity.

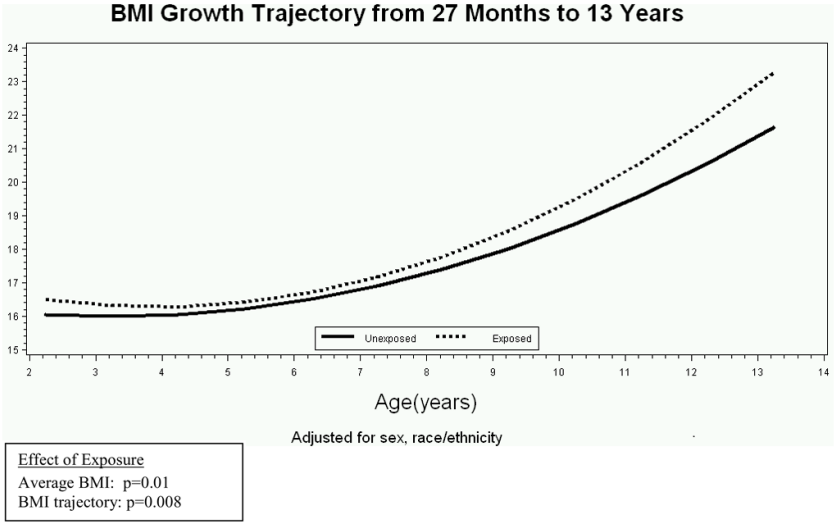

Figure 2.
Mean BMI curves for youth both exposed and unexposed to maternal diabetes *in utero* from 27 months of age to 13 years, adjusted for sex, race/ethnicity.

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Table 1

BMI growth velocity of subjects exposed and unexposed to DM *in utero*, by age-group*

	Unexposed (n=409)		Exposed (n=95)		Difference	P
Age group	**# obs**	**β (SE)**	**# obs**	**β (SE)**	**β (SE)**	
Birth	374		77			
Birth – 8m	826	2.70 (0.17)	245	2.19 (0.29)	−0.51 (0.33)	0.12
9–12m	43	−0.36 (0.05)	11	−0.05 (0.14)	0.31 (0.15)	0.03
13–26m	677	−0.17 (0.18)	201	−0.10 (0.34)	0.07 (0.38)	0.85
27m–3y	311	−0.02 (0.07)	93	−0.22 (0.13)	−0.20 (0.15)	0.19
4–6y	500	0.40 (0.06)	150	0.35 (0.12)	−0.05 (0.14)	0.73
7–9y	632	1.44 (0.08)	207	1.73 (0.17)	0.29 (0.19)	0.13
10–13y	867	3.51 (0.15)	157	4.56 (0.34)	1.05 (0.37)	0.005
Total	4230		1141			

*Adjusted for sex, race/ethnicity.

β expresses change over age range in kg/m^2

Table 2

Estimated effects of exposure to diabetes in utero and selected covariates on childhood BMI growth velocity, from the fully adjusted model

	Birth to 26 months spline		27 months to 14 years	
Parameter	**β (SE)**	**P**	**β (SE)**	**P**
Sex (male)	0.53 (0.14)	0.0001	0.37 (0.17)	0.02
Race/ethnicity				
Hispanic	0.18 (0.15)	0.24	0.07 (0.18)	0.70
AA	0.03 (0.26)	0.91	0.18 (0.31)	0.55
Household income	−0.30 (0.14)	0.04	−0.08 (0.18)	0.65
Maternal education (<high school)	−0.66 (0.45)	0.14	−0.58 (0.58)	0.32
Gestational age (/week)	0.09 (0.03)	0.004	0.06 (0.04)	0.08
Maternal age	−0.03 (0.01)	0.02	−0.02 (0.02)	0.31
Pre pregnancy BMI	0.04 (0.01)	<.0001	0.03 (0.01)	0.03
Overall effect of exposure				
Average BMI		0.21		0.02
BMI trajectory		0.13		0.009

AA= African-American

Results of the fully adjusted model. Separate growth curves are presented for the infancy period of birth to 26 months and childhood period of 27 months to 14 years. See statistical methods for form of the models.