



## Original Contribution

# Pregnancy Glycemia in Mexican-American Women Without Diabetes or Gestational Diabetes and Programming for Childhood Obesity

Samantha F. Ehrlich\*, Lisa G. Rosas, Assiamira Ferrara, Janet C. King, Barbara Abrams, Kim G. Harley, Monique M. Hedderson, and Brenda Eskenazi

\* Correspondence to Dr. Brenda Eskenazi, Center for Environmental Research and Children's Health, School of Public Health, University of California, Berkeley, 1995 University Ave., Suite 265, Berkeley, CA (e-mail: eskenazi@berkeley.edu).

Initially submitted March 19, 2012; accepted for publication July 6, 2012.

In the present study, we estimated the association between pregnancy glucose levels and offspring body mass index (BMI) z scores at 2, 3.5, 5, and 7 years of age, as well as z score trajectories across this age range, among Mexican-American women without diabetes or gestational diabetes. Beginning in 1999–2000, the Center for the Health Assessment of Mothers and Children of Salinas prospectively followed women from Monterey County, California (52 obese and 214 nonobese women) and their children. Plasma glucose values obtained 1 hour after a 50-g oral glucose load comprised the exposure. Offspring BMIs were compared with national data to calculate z scores. Increasing pregnancy glucose levels were associated with increased offspring BMI z scores at 7 years of age; a 1-mmol/L increase in glucose corresponded to an increase of 0.11 (standard deviation = 0.044) z-score units ( $P < 0.05$ ). In nonobese women only, the mean z score over this age range increased with increasing glucose levels. The average BMI z score at 4.5 years of age increased by 0.12 (standard error, 0.059) units for each 1-mmol/L increase in glucose ( $P = 0.04$ ). In obese women only, increasing glucose was associated with increases in BMI z score over time ( $P = 0.07$ ). Whether interventions to reduce glucose values in women free of disease could mitigate childhood obesity remains unknown.

blood glucose; child development; growth and development; obesity; pregnancy

Abbreviations: BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; GDM, gestational diabetes mellitus; LME, linear mixed effects; SD, standard deviation; SE, standard error.

Mexican-American children in the United States are more likely to be overweight or obese than are non-Hispanic white children and, as shown in some studies, than non-Hispanic black children (1–3). Among Mexican-American children, 33% of 2- to 5-year old children and 41% of 6- to 11-year old children are overweight or obese; the corresponding prevalences in non-Hispanic whites are 24% and 29%, respectively (1). Obese children are more likely to become obese adults (4, 5), and Mexican-Americans have increased risks of the comorbidities of obesity, such as diabetes (6) and gestational diabetes (7). Because Mexican Americans are the largest and fastest-growing immigrant group in the United States (8), research is needed to understand the determinants of obesity in this population.

A growing body of research has suggested that the intra-uterine environment may influence later development and morbidity (9, 10). Gestational diabetes mellitus (GDM) has been associated with childhood obesity in several studies of primarily non-Hispanic white (11, 12) or multiethnic (13) populations. It is less clear whether elevated pregnancy glucose values that are below the diagnostic cutpoints for GDM have a similar effect. In women without recognized pregestational diabetes or GDM, an increasing trend in child weight-for-age at 5–7 years across increasing quartiles of maternal glucose has been reported (11). Another study in women without recognized pregestational diabetes or GDM found that those with pregnancy glucose concentrations of 7.2 mmol/L (130 mg/dL) or higher had twice the risk of

having a child who was overweight or obese at 3 years of age than did women with glucose concentrations less than 5.6 mmol/L (100 mg/dL) (14).

Among women without recognized pregestational diabetes or GDM, we sought to determine the relationship between pregnancy glucose levels and offspring body mass index (BMI) *z* scores at 2, 3.5, 5, and 7 years of age. We also examined the association between pregnancy glucose levels and the rate of increase, or velocity, of childhood BMI *z* scores across this age range. The mothers and children were participants in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study, a longitudinal birth cohort study of Mexican Americans.

## MATERIALS AND METHODS

Pregnant women were eligible for the CHAMACOS Study if they sought prenatal care at 1 of 6 participating clinics between October 1999 and October 2000, were at less than 20 weeks of gestation, were 18 years of age or older, were eligible for state-sponsored health care, and intended to deliver at Natividad Medical Center (Monterey County, California). A total of 601 women were enrolled; 485 were followed until the delivery of a full-term ( $\geq 37$  weeks gestation) liveborn singleton.

Plasma glucose levels were measured at the end of each participant's second trimester. Plasma glucose measurements and diagnoses of diabetes and GDM were abstracted from participants' medical records by a registered nurse. We included women without type 1 diabetes mellitus, type 2 diabetes mellitus, or GDM who had a plasma glucose value measured 1 hour after a 50-g oral glucose challenge test performed within the recommended window of 24 to 28 weeks' gestation (15). We excluded 11 women with recognized pregestational diabetes and 1 with unrecognized pregestational diabetes (any glucose measurement  $> 11.1$  mmol/L on more than 1 occasion during pregnancy). We excluded 5 cases of GDM identified by the results of the screening 50-g, 1-hour oral glucose challenge test and diagnostic 100-g, 3-hour oral glucose tolerance test. During this period, GDM was diagnosed according to the National Diabetes Data Group criteria (15), which included a 50-g, 1-hour oral glucose challenge test value of 7.8 mmol/L or higher and at least 2 measurements on the 100-g, 3-hour oral glucose tolerance test meeting or exceeding the following thresholds: fasting, 5.8 mmol/L or higher; 1-hour, 10.5 mmol/L or higher; 2-hour, 9.1 mmol/L or higher; and 3-hour, 8.0 mmol/L or higher. Also excluded was 1 woman who had an abnormal value on the screening test (11.1 mmol/L) but no follow-up 100-g, 3-hour oral glucose tolerance test, 23 women with diagnoses of GDM in their medical records who did not meet the diagnostic criteria (because they received treatment for hyperglycemia), and 113 women whose 50-g, 1-hour oral glucose challenge tests were not performed within the recommended window (15). None of the remaining 331 women met the lower 100-g, 3-hour oral glucose tolerance test thresholds of the American Diabetes Association criteria for GDM (16), and 266 had offspring anthropometric data available at 2, 3.5, 5, or 7 years of age.

Children were weighed and measured without jackets and shoes using a calibrated electronic scale (Tanita Mother-Baby Scale Model 1582 or TBF-300A Body Composition Analyzer, Tanita Corp., Arlington Heights, Illinois) and a stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. BMI *z* scores were calculated from sex- and age-specific data issued by the Centers for Disease Control and Prevention (17).

Mothers were interviewed during pregnancy to obtain information on smoking (yes or no), poverty (above versus at or below the federal poverty level, i.e., an annual income of \$17,650 for a family of 4 (18)), and soda consumption. Abstracted from the medical record were gestational weight gain, gestational age at the prenatal weight measurements (weeks), maternal height, child birthweight (grams), and gestational age at birth (weeks). Gestational age was based on maternal report of last menstrual period for 96%; 1% had an approximate last menstrual period (only month and year reported, day 14 assumed), and the remaining 3% were based on ultrasound. Maternal soda consumption before the screening test was used as a proxy for prepregnancy soda consumption (19). Soda consumption was ascertained at the end of the second trimester (mean gestational age, 26.7 weeks, standard deviation (SD), 1.9;  $n = 255$ ); women were asked how often they drank a 12-ounce can of soda or other soft drink (nondiet) during the last 3 months, and the frequency was coded times per week.

Prepregnancy weight was obtained from the medical record (89%), from a self-report on the pregnancy questionnaire (8%), from an early prenatal weight measurement ( $< 13$  weeks gestational age; 1%), or by a regression that utilized all prenatal weight measurements and corresponding gestational ages (2%). In a subset of participants for whom prepregnancy weight data were available in the medical record, pregnancy questionnaire, and an early prenatal weight measurement ( $n = 139$ ; 52%), prepregnancy weight from the medical record was significantly correlated with early prenatal weight (Spearman's  $\rho = 0.96$ ;  $P < 0.0001$ ); self-reported prepregnancy weight was also significantly correlated with early prenatal weight (Spearman's  $\rho = 0.95$ ;  $P < 0.0001$ ). Only gestational weight gain that occurred before the exposure could confound the association of interest; thus, prepregnancy weight was subtracted from the nearest prenatal weight measurement taken before the glucose test to calculate the amount of weight gained up until the time of the glucose test.

Multiple linear regression analyses were used to estimate the association between pregnancy glucose level, measured 1 hour after a 50-g oral glucose load, and offspring BMI *z* scores at 2, 3.5, 5, and 7 years of age. We also estimated the association between pregnancy glucose measurements and mean BMI *z* scores over the age range, as well as BMI *z*-score velocity (the rate of change in BMI *z* score over time), using linear mixed effects (LME) models. Pregnancy glucose level was examined as a continuous variable.

A directed acyclic graph (20) guided the selection of adjustment variables (Web Figure 1, available at <http://aje.oxfordjournals.org/>). Multiple linear regression models were adjusted for prepregnancy obesity (BMI  $\geq 30$ ), times per week soda was consumed before the glucose test (continuous),

gestational weight gained before the glucose test (continuous), gestational age at the weight measurement (continuous), smoking, poverty, infant birthweight (continuous), and the child's absolute age in months (continuous) at follow-up. Models that included prepregnancy BMI (continuous) instead of prepregnancy obesity gave equivalent results. Estimates were unaltered by additional adjustment for gestational age at birth; therefore, the results presented were not adjusted for this variable (21). Lifestyle characteristics are shared among family members, so sensitivity analyses with additional adjustment for the children's consumption of sugar-sweetened beverages (22) and/or television watching (23) were conducted; these variables served as proxies for the corresponding behavior during pregnancy, which were the "true" confounders.

We verified the assumptions of linear regression and investigated potential effect modification by prepregnancy BMI (continuous) and prepregnancy obesity (BMI  $\geq 30$ ). Prepregnancy obesity impacts fetal growth and development by altering the metabolic adjustments that accompany normal gestation, resulting in fetal exposure to excessive fuel sources and increasing the risk of obesity (24, 25). At each time point, cross products were added, one at a time, to the fully adjusted model; a *t* score with  $P < 0.15$  (2-tailed) was considered significant. The prepregnancy obesity cross product was significant at 2 years of age ( $P = 0.14$ ), and the prepregnancy BMI cross product was significant at 5 years of age ( $P = 0.12$ ). Therefore, results stratified by prepregnancy obesity are also presented.

The LME models of longitudinal data accounted for intra-subject correlation between repeated measurements and allowed for a different number of follow-up observations (26). Maximum likelihood was the method of estimation, and an unstructured working covariance matrix for the random effects parameters (intercept and slope) was chosen. Pregnancy glucose levels and the adjustment variables were modeled as fixed effects.

Because of increased risk for obesity among children born to obese women (24, 25), we hypothesized differential growth velocities for the offspring of women who were obese before pregnancy and those who were not; separate LME models were constructed among obese (BMI  $\geq 30$ ;  $n = 52$ ) and nonobese ( $n = 214$ ) women. The Akaike information criterion statistic facilitated model selection; the final models for obese and nonobese women included linear and quadratic terms for the children's ages ( $P < 0.001$ ) and an age-glucose cross product to estimate the rate of change in BMI *z* scores over time that were associated with a 1-mmol/L increase in pregnancy glucose (BMI *z*-score velocity). Locally weighted scatterplot smoothing was used to graphically display BMI *z*-score trajectories by glucose tertile separately for nonobese and obese women.

To assess selection bias, we compared women included in the analyses with those who were excluded because they had their glucose test outside of the recommended window or were missing offspring anthropometric data at follow up ( $n = 178$ ) in regard to the following: prepregnancy BMI, years in the United States, educational level, poverty, parity, smoking, and age at delivery. We also conducted analyses weighted by the inverse probability that a mother-child pair

would remain in the cohort for at least 1 follow-up measurement. SuperLearner (27), a prediction algorithm, was used to predict whether a pair remained in the cohort.

All analyses were conducted in SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina), and plots were produced in Stata, version 10.1 (StataCorp LP, College Station, Texas). SuperLearner was run in R, version 2.12.1 (The R Foundation for Statistical Computing, Vienna, Austria). Study participants provided written informed consent, and all research activities were approved by the University of California–Berkeley Committee for the Protection of Human Subjects.

## RESULTS

Women who were excluded because they had their glucose test outside of the recommended window or were missing offspring anthropometric data at follow up ( $n = 178$ ) did not differ from the study sample ( $n = 266$ ) in terms of prepregnancy BMI, years in the United States, educational level, poverty, parity, smoking, or age. Characteristics of the analytic cohort of 266 mother-child pairs are displayed in Table 1. Only 20% of the mothers had completed high school, and 63% had household incomes at or below the poverty threshold. Mothers tended to be young (mean maternal age = 26.0 years, SD, 5.0) and overweight (mean prepregnancy BMI = 26.8, SD, 5.0). Mothers consumed an average of 1.6 (SD, 2.3) servings of nondiet soda per week ( $n = 263$  women with available data) and gained an average of 5.2 (SD, 4.3) kg before the glucose test ( $n = 265$  women with available data; mean gestational age at the weight measurement = 22.3 weeks, SD, 5.3). In the offspring, the mean BMI *z* score was 0.49 (SD, 1.09) at 2 years ( $n = 240$ ), 1.09 (SD, 1.05) at 3.5 years ( $n = 213$ ), 1.21 (SD, 1.03) at 5 years ( $n = 213$ ), and 1.16 (SD, 1.03) at 7 years ( $n = 217$ ) of age.

Pregnancy glucose values significantly predicted offspring BMI *z* scores at 5 and 7 years of age independently of prepregnancy obesity, soda consumption, gestational weight gain before the glucose test, and infant birthweight. Each 1-mmol/L increase in glucose level corresponded to an increase of 0.10 (standard error (SE), 0.047) BMI *z*-score units at 5 years of age ( $P = 0.03$ ; Table 2) and 0.11 (SE, 0.044) BMI *z*-score units at 7 years of age ( $P = 0.01$ ; Table 2). No associations were observed at younger ages in the pooled analyses. Prepregnancy obesity predicted increases in BMI *z* scores at 5 and 7 years of age (Table 2) significantly and independently of glucose. In analyses stratified by prepregnancy obesity (Table 2), glucose values significantly predicted offspring BMI *z* scores at 2 and 7 years of age in nonobese women only. In nonobese women, each 1-mmol/L increase in glucose value corresponded to an increase of 0.11 (SE, 0.049) BMI *z*-score units at 2 years of age ( $P = 0.03$ ) and 0.11 (SE, 0.051) BMI *z*-score units at 7 years of age ( $P = 0.03$ ); the estimates at 3.5 and 5 years of age were similar in magnitude but nonsignificant. In obese women only, no associations were observed (Table 2).

Figure 1 presents smoothed scatterplots of offspring BMI *z*-score trajectories across the age range, demonstrating differences in growth patterns for the offspring of nonobese

**Table 1.** Cohort Characteristics of 266<sup>a</sup> Mexican-American Mother-Child Pairs From the CHAMACHOS Study Cohort, 1999–2000

Characteristic	No. of Participants	%	Mean (SD)
Prepregnancy BMI <sup>b</sup>			
Underweight (<18.5)	2	0.8	
Normal (18.5–24.9)	105	39.5	
Overweight (25.0–29.9)	107	40.2	
Obese (≥30.0)	52	19.6	
Years in the United States			
≤5	140	52.6	
>5	126	47.4	
Maternal educational level			
≤6th grade	121	45.5	
7–12th grade	91	34.2	
≥High school graduate	54	20.3	
At or below the poverty line	168	63.2	
Parity			
0	88	33.1	
1	85	32.0	
2	54	20.3	
≥3	39	14.7	
Smoked during pregnancy	16	6.0	
Soda consumed before the glucose test ( <i>n</i> = 263)			
Never	105	39.9	
1–3 times per month	29	11.0	
1–2 times per week	76	28.9	
3–6 times per week	18	7.9	
Every day	32	12.2	

Table continues

and obese women. For nonobese women, the stratum-specific glucose tertile ranges were 2.9–4.9, 5.0–6.3, and 6.4–10.1 mmol/L; the corresponding ranges for obese women were 3.3–5.3, 5.4–6.4, and 6.8–9.8 mmol/L. In the fully adjusted LME for nonobese women (*n* = 213), the observed increase in mean BMI *z* score across the age range with increasing glucose was statistically significant (*P* = 0.04); the estimated average BMI *z* score at 4.5 years of age increased by 0.12 (SE, 0.059) BMI *z*-score units for each mmol/L increase in glucose. In the fully adjusted LME for obese women (*n* = 49), the observed increase in BMI *z*-score

**Table 1.** Continued

Characteristic	No. of Participants	%	Mean (SD)
Maternal age at delivery, years			
18–24	121	45.5	
25–29	90	33.8	
30–34	34	12.8	
35–45	21	7.9	
Offspring BMI <i>z</i> score ≥95%			
2 years of age ( <i>n</i> = 240)	41	17.1	
3.5 years of age ( <i>n</i> = 213)	72	33.8	
5 years of age ( <i>n</i> = 213)	75	35.2	
7 years of age ( <i>n</i> = 217)	82	37.8	
Glucose screening value, mmol/L			5.9 (1.5)
Gestational age at screening test, weeks			26.4 (1.1)
Gestational age at soda consumption assessment, weeks ( <i>n</i> = 255)			26.7 (1.9)
Gestational weight gained before the glucose test, kg ( <i>n</i> = 265)			5.2 (4.3)
Gestational age at weight measurement, weeks ( <i>n</i> = 265)			22.3 (5.3)
Birthweight, g			3,496.7 (440.0)
Gestational age at delivery, weeks			39.2 (1.2)

Abbreviations: BMI, body mass index; CHAMACHOS, Center for the Health Assessment of Mothers and Children of Salinas; SD, standard deviation.

<sup>a</sup> Unless otherwise noted.

<sup>b</sup> Weight (kg)/height (m)<sup>2</sup>.

velocity with increasing glucose was nonsignificant (*P* = 0.07); the estimated rate of increase was 0.034 (SE, 0.019) BMI *z*-score units per year for each 1-mmol/L increase in glucose.

The results of models that included additional adjustment for the children's television watching or consumption of sugar-sweetened beverages and television watching combined were identical to those presented in Table 2 (data not shown). The linear regression results obtained from the inverse probability-weighted analyses were similar to the results of the unweighted analyses (Web Table 1); in the pooled sample, the association between pregnancy glycemia and BMI *z* score at 5 years of age was similar in magnitude

**Table 2.** Linear Regression Coefficients for the Association Between Pregnancy Glucose and Offspring Body Mass Index *z* Score, the CHAMACHOS Study Cohort, 1999–2000

	No.	Unadjusted		Adjusted <sup>a</sup>	
		$\beta$	SE	$\beta$	SE
<i>Pooled</i>					
2 years of age	234				
Glucose		0.078	0.047	0.078	0.046
Prepregnancy obesity				0.35	0.18
3.5 years of age	201				
Glucose		0.060	0.049	0.063	0.050
Prepregnancy obesity				0.28	0.20
5 years of age	204				
Glucose		0.11*	0.046	0.10*	0.047
Prepregnancy obesity				0.42*	0.19
7 years of age	214				
Glucose		0.13**	0.046	0.11*	0.044
Prepregnancy obesity				0.57**	0.17
<i>Stratified by Prepregnancy Obesity</i>					
<b>Obese</b>					
2 years of age	44	−0.073	0.12	−0.061	0.13
3.5 years of age	34	−0.11	0.13	−0.15	0.13
5 years of age	37	0.12	0.11	0.11	0.12
7 years of age	42	0.093	0.088	0.11	0.094
<b>Nonobese</b>					
2 years of age	190	0.11*	0.049	0.11*	0.049
3.5 years of age	167	0.095	0.053	0.094	0.054
5 years of age	167	0.10*	0.050	0.099	0.052
7 years of age	172	0.13**	0.051	0.11*	0.051

Abbreviations: CHAMACHOS, Center for the Health Assessment of Mothers and Children of Salinas; SE, standard error.

\*  $P < 0.05$ , \*\*  $P < 0.01$  for 2-tailed *t*-score test.

<sup>a</sup> Adjusted for soda consumption before the glucose test, gestational weight gained before the glucose test, gestational age at the prenatal weight measurement, smoking, poverty, infant birthweight, and child's absolute age at the follow-up measurements.

but attained only borderline significance ( $P = 0.05$ ). The inverse probability-weighted linear regression analyses stratified by prepregnancy obesity gave results comparable to those from the unweighted analyses (Web Table 1). The results of the inverse probability-weighted LME models were identical to the unweighted results (data not shown).

## DISCUSSION

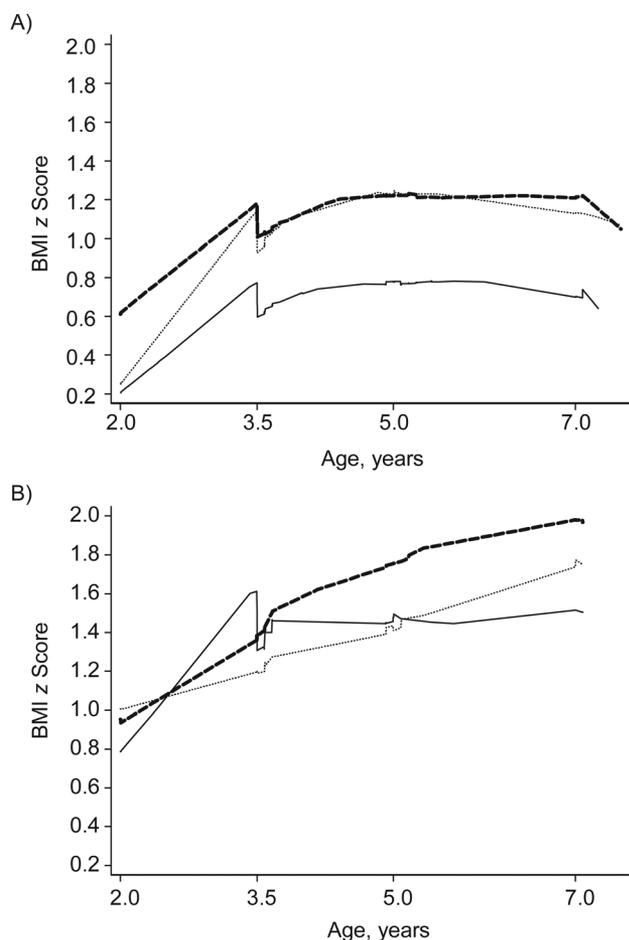
In Mexican-American women without recognized pregestational diabetes or GDM, we found a significant association between increasing pregnancy plasma glucose values, assessed during a single 50-g oral glucose challenge test in

midpregnancy, and increasing offspring BMI *z* score at 7 years of age. In nonobese women without recognized pregestational diabetes or GDM, in utero exposure to increasing glucose levels was associated with childhood obesity at ages 2 and 7 years, and on average, children exposed to higher glucose levels demonstrated increased *z* scores over the course of this age range. This study fills important gaps in the literature on the developmental origins of obesity in a population that is at high risk for childhood obesity.

To our knowledge, only 2 previous studies have examined whether increasing levels of maternal pregnancy glucose are associated with childhood anthropometrics in the offspring of women without recognized pregestational diabetes or GDM. In a multiethnic study of mother-child pairs enrolled in a health maintenance organization, Hillier et al. (11) reported a positive trend in weight-for-age greater than the 85th and 95th percentiles across increasing quartiles of maternal glucose assessed 1 hour after a 50-g oral glucose load. Children 5 to 7 years of age were combined for analyses, so associations could not be estimated separately by age; the study also did not examine growth trajectories. Mothers participating in the Pregnancy Infection and Nutrition Study also had pregnancy glucose concentrations assessed 1 hour after a 50-g oral glucose load; compared with women with glucose levels less than 5.6 mmol/L (100 mg/dL), those with glucose levels of 7.2 mmol/L (130 mg/dL) or higher had children with significantly higher BMI *z* scores at 3 years of age (14). Unlike women in the CHAMACHOS Study, those in the Pregnancy Infection and Nutrition Study were mostly white, well-educated, and in an upper income bracket.

Our results are consistent with previous reports that suggested an association between exposure to maternal diabetes in utero and increased offspring adiposity in late childhood. Offspring exposed to maternal diabetes in utero tend to be larger at birth, but similar to the general population by 1 year of age, they begin demonstrating increases in weight relative to height by 5 years of age and are more likely to be overweight or obese by 8 years of age (28). The National Collaborative Perinatal Project (12) has similarly reported that the offspring of women with GDM had offspring with higher BMI *z* scores at 7 years of age compared with the offspring of women without GDM. To our knowledge, this is the first study to report an association at 2 years of age among non-obese women free of recognized disease.

Our findings are biologically plausible. Women with mildly high pregnancy glucose levels who are free of recognized disease may have children with increased body mass as a result of mechanisms similar to those hypothesized for the offspring of women with diabetes and GDM. Increasing levels of maternal glycemia are associated with increasing fetal hyperinsulinemia (29) and neonatal adiposity (30). The third trimester of pregnancy is known to be a critical period for adipose cell hyperplasia (31), and increased maternal glycemia may also result in fetal exposure to increased amounts of lipid substrates during this critical period (32). It has been hypothesized that maternal hyperglycemia and fuel metabolism in pregnant women may have long-term effects on offspring by modifying phenotypic gene expression in terminally differentiated cells during intrauterine development (33). It is



**Figure 1.** Smoothed scatterplots of offspring body mass index (BMI; weight (kg)/height (m)<sup>2</sup>) z-score trajectories from 2 to 7 years of age for nonobese (BMI <30) and obese (BMI ≥30) women by pregnancy glucose tertile, the Center for the Health Assessment of Mothers and Children of Salinas Study Cohort, 1999–2000. A) BMI z-score trajectories of the nonobese women. The solid line represents nonobese women in the lowest tertile of pregnancy glucose measurement (2.9–4.9 mmol/L), the dotted line represents those in the middle tertile (5.0–6.3 mmol/L), and the dashed line represents those in the upper tertile (6.4–10.1 mmol/L). B) BMI z-score trajectories of the obese women. The solid line represents obese women in the lowest tertile of pregnancy glucose measurement (3.3–5.3 mmol/L), the dotted line represents those in the middle tertile (5.4–6.4 mmol/L), and the dashed line represents those in the upper tertile (6.8–9.8 mmol/L).

possible that similar gene expression modification may also occur in women without overt disease.

Although we identified no previous studies that examined the trajectories of childhood growth by pregnancy glucose and obesity in women without recognized pregestational diabetes or GDM, our results are consistent with those from a study examining the association between in utero exposure to GDM and BMI trajectory from birth to 13 years of age (34) that found that the overall sex- and race/ethnicity-adjusted BMI trajectory was significantly higher between the ages of 27 months and 13 years in youths exposed to GDM; this

difference was primarily driven by an increased BMI growth velocity from 10 to 13 years of age in those exposed to GDM. No differences were observed in infancy or early childhood.

In our analyses of BMI z-score trajectory among non-obese women, there was an association between increasing pregnancy glucose and higher offspring BMI z score, on average, across the age range. The effect of in utero exposure to increasing glucose levels would likely be easier to detect in the offspring of nonobese women, who are not exposed to excessive fuel substrates as a result of maternal obesity (24). In obese women, the association between increasing pregnancy glucose and an increased rate of BMI z score increase over time nearly attained statistical significance. In fetuses already exposed to excessive fuel substrates because of maternal obesity, in utero exposure to higher glucose levels would likely compound overnutrition and exacerbate programming for subsequent obesity. Significant associations between pregnancy glucose and BMI z-score velocity may not have been recognized if, similar to what was seen in the offspring of women with pregestational diabetes and GDM, the effects of pregnancy glucose among obese women are not detectable until later childhood or puberty. Data from larger cohorts with longer follow up would contribute greatly to answering these questions.

The prospective design is a clear strength of the present study, as it is essential for examining the effect of any in utero exposure on subsequent obesity. However, there are limitations to consider. We lacked data on physical activity levels in the women and only partially adjusted the models for diet; thus, unmeasured lifestyle factors may account for some or all of the associations described. Prepregnancy weight was most likely underreported, and thus some women may have been misclassified as nonobese. This suggests that our estimates for the association between prepregnancy obesity and offspring BMI z scores are conservative. The small sample size resulted in diminished power to detect interactions and some associations, especially in analyses limited to obese women. The results of the pooled analyses were also largely driven by the nonobese. In nonobese women, coefficient estimates were stable over time; the non-significant findings at 3.5 and 5 years of age may be attributable to reduced sample sizes at those time points.

In an at-risk cohort of women of Mexican descent, we found that exposure to higher levels of plasma glucose during pregnancy was associated with an increased risk of having offspring who were obese at 7 years of age. In non-obese women, there was also an association between higher levels of pregnancy plasma glucose and increased average offspring BMI z scores from 2 to 7 years of age. Randomized control trials investigating lifestyle interventions to reduce pregnancy glucose values in women free of recognized disease are needed to determine the potential efficacy of such efforts in mitigating subsequent childhood obesity.

#### ACKNOWLEDGMENTS

Author affiliations: Center for Environmental Research and Children's Health, School of Public Health, University of

California, Berkeley, Berkeley, California (Samantha F. Ehrlich, Kim G. Harley, Brenda Eskenazi); Division of Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, California (Samantha F. Ehrlich, Barbara Abrams, Brenda Eskenazi); Division of Research, Kaiser Permanente Northern California, Oakland, California (Samantha F. Ehrlich, Assiamira Ferrara, Monique M. Hedderson); Prevention Research Center, Stanford School of Medicine, Stanford, California (Lisa G. Rosas); and Children's Hospital and Research Center, Oakland, California (Janet C. King).

This work was supported by dissertation assistance to S.E. from the Russell M. Grossman Endowment and the Reshetko Family Scholarship, as well as grants from the Environmental Protection Agency (RD 83171001) and the National Institute of Environmental Health Sciences (PO1ES009605) to B.E.

We wish to thank our staff and community partners. We are especially grateful to Dr. Raul Aguilar, Dr. Jonathan Chevrier, Katherine Kogut, Kristin Tyler, and Michelle G. Vedar of the Center for Environmental Research and Children's Health at the University of California, Berkeley, and Dr. Charles P. Quesenberry, Jr., at the Kaiser Permanente Division of Research for guidance on the analysis and presentation of these data.

Conflict of interest: none declared.

## REFERENCES

- Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA*. 2012;307(5):483–490.
- Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295(13):1549–1555.
- Whitaker RC, Orzol SM. Obesity among US urban preschool children: relationships to race, ethnicity, and socioeconomic status. *Arch Pediatr Adolesc Med*. 2006;160(6):578–584.
- Guo SS, Wu W, Chumlea WC, et al. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *Am J Clin Nutr*. 2002;76(3):653–658.
- Deshmukh-Taskar P, Nicklas TA, Morales M, et al. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. *Eur J Clin Nutr*. 2006;60(1):48–57.
- Sundquist J, Winkleby MA. Cardiovascular risk factors in Mexican American adults: a transcultural analysis of NHANES III, 1988–1994. *Am J Public Health*. 1999;89(5):723–730.
- Hollingsworth DR, Vaucher Y, Yamamoto TR. Diabetes in pregnancy in Mexican Americans. *Diabetes Care*. 1991;14(7):695–705.
- US Census Bureau. *The American Community, Hispanics: 2004, American Community Survey Reports*. Washington, DC: US Department of Commerce; 2007.
- Barker DJ. The origins of the developmental origins theory. *J Intern Med*. 2007;261(5):412–417.
- Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med*. 2000;9(1):83–88.
- Hillier TA, Pedula KL, Schmidt MM, et al. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care*. 2007;30(9):2287–2292.
- Baptiste-Roberts K, Nicholson WK, Wang NY, et al. Gestational diabetes and subsequent growth patterns of offspring: the National Collaborative Perinatal Project. *Matern Child Health J*. 2012;16(1):125–132.
- Crume TL, Ogden L, West NA, et al. Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes Among Children (EPOCH) Study. *Diabetologia*. 2011;54(1):87–92.
- Deierlein AL, Siega-Riz AM, Chantala K, et al. The association between maternal glucose concentration and child BMI at age 3 years. *Diabetes Care*. 2011;34(2):480–484.
- Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes*. 1979;28(12):1039–1057.
- American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care*. 2000;23(suppl 1):S77–S79.
- Centers for Disease Control and Prevention. *A SAS Program for the CDC Growth Charts*. Atlanta, GA: Centers for Disease Control and Prevention; 2011. (<http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm>). (Accessed October 24, 2011).
- US Census Bureau. *Poverty Thresholds 2000*. Washington, DC: US Census Bureau; 2000. (<http://www.census.gov/hhes/www/poverty/data/threshld/thresh00.html>). (Accessed October 24, 2011).
- Chen L, Hu FB, Yeung E, et al. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. *Diabetes Care*. 2009;32(12):2236–2241.
- Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37–48.
- Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol*. 2011;174(9):1062–1068.
- Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. 2007;97(4):667–675.
- Tremblay MS, LeBlanc AG, Kho ME, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. *Int J Behav Nutr Phys Act*. 2011;8:98.
- King JC. Maternal obesity, metabolism, and pregnancy outcomes. *Annu Rev Nutr*. 2006;26:271–291.
- Smith J, Cianflone K, Biron S, et al. Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J Clin Endocrinol Metab*. 2009;94(11):4275–4283.
- Finucane MM, Samet JH, Horton NJ. Translational methods in biostatistics: linear mixed effect regression models of alcohol consumption and HIV disease progression over time. *Epidemiol Perspect Innov*. 2007;4:8.
- van der Laan MJ, Polley EC, Hubbard AE. Super learner. *Stat Appl Genet Mol Biol*. 2007;6(1):Article25.
- Silverman BL, Rizzo T, Green OC, et al. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes*. 1991;40(suppl 2):121–125.
- Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358(19):1991–2002.
- The HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009;58(2):453–459.

31. Brook CG. Evidence for a sensitive period in adipose-cell replication in man. *Lancet*. 1972;2(7778):624–627.
32. Kitajima M, Oka S, Yasuhi I, et al. Maternal serum triglyceride at 24–32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens. *Obstet Gynecol*. 2001;97(5):776–780.
33. Freinkel N. Banting Lecture 1980: Of pregnancy and progeny. *Diabetes*. 1980;29(12):1023–1035.
34. Crume TL, Ogden L, Daniels S, et al. The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH Study. *J Pediatr*. 2011;158(6):941–946.