



# Maternal Hyperglycemia During Pregnancy Predicts Adiposity of the Offspring

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## OBJECTIVE

To investigate associations between maternal pregnancy hyperglycemia, gestational diabetes mellitus (GDM), and offspring adiposity.

## RESEARCH DESIGN AND METHODS

We evaluated these associations in a longitudinal study of 421 mother-daughter pairs at Kaiser Permanente Northern California. Maternal pregnancy glucose values were obtained from maternal medical records. Outcomes included three measures of girls' adiposity, measured annually: 1)  $\geq 85$ th age-specific percentile for BMI; 2) percent body fat (%BF); and 3) waist-to-height ratio (WHR).

## RESULTS

Adjusting for maternal age at delivery, race/ethnicity, pregravid BMI, girl's age, and girl's age at onset of puberty, having a mother with GDM increased a girl's risk of having a BMI  $\geq 85$ th percentile or having %BF or WHR in the highest quartile (Q4), compared with those in the lowest quintile of blood glucose (odds ratio [OR] 3.56 [95% CI 1.28–9.92]; OR 3.13 [95% CI 1.08–9.09]; and OR 2.80 [95% CI 1.00–7.84], respectively). There was a significant interaction between the presence of GDM and pregravid BMI; girls whose mothers had both risk factors had the highest odds of having a BMI  $\geq 85$ th percentile (OR 5.56 [95%CI 1.70–18.2]; Q4 %BF, OR 6.04 [95%CI 1.76–20.7]; and Q4 WHR, OR 3.60 [95%CI 1.35–9.58]). Similar, although weaker, associations were found in the association between hyperglycemia and offspring adiposity.

## CONCLUSIONS

Girls who were exposed to maternal GDM or hyperglycemia in utero are at higher risk of childhood adiposity; risk increases if the mother is overweight or obese. Screening and intervention for this high-risk group is warranted to slow the intergenerational transmission of obesity and its sequelae.

By age 2 years, almost one-third of U.S. children are overweight or obese (1), and childhood obesity strongly predicts adult obesity and chronic diseases (2). The perinatal period offers a critical opportunity for obesity prevention: the programming of obesity starts very early, even in utero, where gestational and perinatal factors affect the offspring's obesity trajectory and metabolic imprinting (3). The White House Task Force on Childhood Obesity (4) and the Surgeon General (5) recommend promoting effective perinatal interventions in an effort to interrupt the intergenerational cycle of obesity. Early prevention is critical because once established, reversal of obesity is often inefficient, ineffective, and costly (6,7).

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It has been hypothesized that fetal overnutrition (i.e., excess maternal fuels including higher blood glucose levels) causes permanent fetal changes, leading to increased risk of obesity and insulin resistance later in life (8,9). Several previous studies provide evidence that children born with intrauterine exposure to type 2 diabetes or gestational diabetes mellitus (GDM) are at increased risk for childhood obesity and type 2 diabetes later in life and that these risks are higher than would be predicted from genetics alone (10–17). However, results have been inconsistent, and the studies have had several limitations (18). For instance, most previous studies used offspring BMI alone as a measure of obesity. However, it is critical to determine the percent of body fat that accounts for total BMI, as BMI is not an accurate indicator of body fat (i.e., individuals with greater muscle mass will have higher BMIs). Because body fat is a tissue with endocrine and immune functions (19), more accurately assessing it is critical, as a higher percentage may predict metabolic disorders such as insulin resistance and metabolic syndrome (20). Also, abdominal fat is more active metabolically than peripheral fat and is more strongly associated with the aforementioned adult chronic conditions and cardiovascular disease (21). Thus, a better understanding of the risk factors associated with development of abdominal obesity and greater adiposity (% fat) may have important public health implications. Second, most previous studies focused on the effect of diabetes or GDM; little is known regarding the effects of subclinical maternal pregnancy hyperglycemia on childhood adiposity. Lastly, few prior studies have included important covariates such as maternal pregravid obesity, child birth weight, and pubertal development data.

Hyperglycemia during pregnancy is modifiable, treatable, and preventable. To further our efforts to design high-yield targets for intervention, we evaluated the association between maternal glycemic level during pregnancy and measures of adiposity in female offspring, including BMI, abdominal obesity, and percent of total body fat. The analyses were conducted in a longitudinal study of multiethnic, adolescent girls in northern California drawn from the

membership of a large prepaid health plan with demographic characteristics similar to the general population (22).

## RESEARCH DESIGN AND METHODS

This study was carried out as part of the Puberty Studies of the National Institute of Environmental Health Sciences/National Cancer Institute Breast Cancer and the Environment Research Program, three cooperative studies examining determinants of early puberty in prospective cohort studies (23). The present analysis used data from one of these epidemiologic projects based in the San Francisco Bay area, the Cohort Study of Young Girls' Nutrition, Environment, and Transitions (CYGNET). Written informed consent from the parents, and assent from the children, was obtained. The study protocol was approved by the Kaiser Permanente Institutional Review Board.

### Participants and Procedure

This study recruited 444 girls and their caregivers (96% biological mothers), currently members of Kaiser Permanente Northern California (KPNC). Details of the study protocol have been described previously (24). Briefly, girls were 6–8 years old at baseline and ethnically diverse. At each annual clinic visit (mean follow-up in this analysis: 3.8 years [range 2–6 years]), anthropometric measurements and Tanner staging for breast and pubic hair development were assessed. Information was collected in various phases through interviews conducted with caregivers and as well with the girls themselves when they were old enough (age 10–12 y) to provide their own information.

### Measurements

#### Exposure Variables

**Maternal Pregnancy Glucose Levels.** Each girl's medical record was linked to her mother's medical record. At KPNC, 95% of pregnant women undergo the recommended 50-g, 1-h glucose challenge test for GDM screening (25) during gestational weeks 24–28 (hereafter referred to as the screening test). All plasma glucose measurements were performed using the hexokinase method by the regional laboratory of KPNC. This laboratory participates in the College of American Pathologists' accreditation and monitoring program. Screening test results were categorized into quintiles. The ranges of plasma glucose

levels for each of the quintile categories were:  $\leq 90$ , 90–103, 104–118, 119–140, and  $\geq 141$  mg/dL. The highest quintile corresponded with the cutoff point used at KPNC to define abnormal screening (1-h glucose  $\geq 140$  mg/dL), and therefore women in this group underwent the diagnostic, 100-g, 3-h oral glucose tolerance test.

GDM was defined according to the Carpenter and Coustan thresholds (26) for the diagnostic test.

Maternal pregravid BMI was calculated as (weight in kg)/(height in meters squared) from self-reported weight and height obtained from the CYGNET Study questionnaire. We categorized the women as normal weight (BMI  $< 25.0$  kg/m<sup>2</sup>), overweight (BMI 25.0 to  $\leq 30.0$  kg/m<sup>2</sup>), and obese (BMI  $\geq 30.0$  kg/m<sup>2</sup>).

### Outcomes

**Offspring BMI.** The annual study clinic visit included several anthropometric measurements. Girls' height was measured to the nearest 0.1 cm, using a mounted wall stadiometer, with the participant in stocking feet and head in the neutral position. Weight was measured without shoes and in light clothing and was rounded to the nearest 0.5 kg. BMI percentile and z-score were calculated in comparison with the appropriate age- (and sex-) specific Centers for Disease Control and Prevention year 2000 standard population distribution (27).

**Waist-to-Height Ratio.** Waist circumference was measured twice at the umbilicus, and the difference between the two measurements was calculated. If the difference was  $> 1$  cm, then a third measurement was taken, and the average for these two or three measurements was used for analysis. Hip circumference was measured at the widest part of the hips following a similar protocol. Waist-to-height ratio (WHR = waist/height) was calculated as a measure of abdominal obesity.

**Percent of Total Body Fat.** Percent of total body fat was estimated from bioelectrical impedance analysis from the Tanita scale, which uses a small electrical current from foot to foot to estimate adiposity.

### Covariates

Girls' demographic information, baseline dietary (percent kcal from fat and total daily energy intake), and physical activity information (using average daily metabolic equivalent), as well as maternal

demographics (income and education) and smoking status during pregnancy, were obtained from the CYGNET questionnaires. Girl's ethnicity was reported by the parent or caregiver and categorized as: African American or black, Latina, Asian, or non-Hispanic white. Pubertal onset was assessed using Tanner staging, an established five-stage classification scheme (28), performed by trained personnel (L.C.G.).

### Statistical Analyses

Data were analyzed using SAS statistical software version 9.3 (SAS Institute, Cary, NC). The demographic and lifestyle characteristics of mothers and daughters were compared among quintile categories of mother's pregnancy glucose levels using ANOVA for continuous variables and  $\chi^2$  test for categorical variables. To estimate the association between maternal pregnancy plasma glucose levels on daughters' obesity for each year of follow-up, we used the generalized estimating equation method, which takes into account correlations among intraindividual outcomes in repeated measures—in this case, repeat assessments of adiposity over 6 years of follow-up.

We defined high adiposity using several measures:  $\geq 85$ th percentile BMI for age, fourth (highest) quartile (Q4) for percent body fat (%BF), and Q4 for WHR. Maternal pregnancy glucose levels were categorized by quintiles of the glucose value, and those in the second to fifth quintile were compared with women in the first (lowest) quintile category (referent). Women in the fifth quintile were categorized into GDM versus no GDM groups. The main models were adjusted for race/ethnicity, maternal pregravid BMI (continuous), girls' age (months), maternal age at delivery (years), and age at onset of puberty (months; i.e., Tanner stages 2+ for breast and pubic hair development).

Second, we investigated whether there was an interaction between maternal pregravid obesity and maternal pregnancy glucose levels on offspring adiposity. For this analysis, girls with mothers with normal pregravid BMI and lowest quintile of pregnancy glucose level (referent) were compared with those with one or two of these risk factors (higher glucose and/or pregravid obesity).

As a supplementary analysis, we examined the role of birth weight on the

pathway between maternal glucose or obesity and offspring obesity. We included birth weight (as continuous as well as categorical: macrosomia  $>4,000$  g; normal weight; and low birth weight  $<2,500$  g) in the model to see if the main association was attenuated.

## RESULTS

### Participant Characteristics

Of the 444 participants, we excluded 23 mother-daughter pairs who were missing maternal pregnancy glucose values, resulting in 421 pairs with baseline information included in the analysis. Table 1 presents the characteristics of the mothers. There were no significant differences for education, income, BMI, or smoking during pregnancy by glucose levels. A total of 27 women had GDM (26 in the fifth quintile and 1 in the fourth quintile). There was a nonsignificant trend for older maternal age at delivery being associated with higher glucose values.

Table 2 presents the characteristics of the girls at baseline and at birth. Older gestational age at birth and higher total daily energy and fat intake among girls was associated with mothers who had lower glucose values during pregnancy.

### Primary Analyses

#### Association Between Maternal Pregnancy Glucose Levels and Girls' Adiposity

Table 3 presents associations between maternal pregnancy glucose levels with girls' adiposity, controlling for race/ethnicity, maternal pregravid BMI, girls' age, Tanner stages, and maternal age at delivery. While accounting for within-subject correlation among the repeated measures, girls whose mothers had the highest quintile of pregnancy glucose were at significantly increased odds of having BMI  $\geq 85$ th percentile (odds ratio [OR] 2.28 [95% CI 1.08–4.84]), being in the upper quartile (Q4) of %BF (OR 2.51 [95% CI 1.16–5.40]), and Q4 of WHR (OR = 2.48 [95% CI 1.17–5.22]) compared with girls whose mother were in the lowest glucose level (Q1). Test for trends across glucose levels were statistically significant for %BF and were borderline for WHR.

#### Presence of GDM

When women in the highest quintile of glucose were stratified by presence/absence of GDM (Table 3), the association

with girls' adiposity measures was consistently stronger among those with GDM compared with those without (OR 3.56 [95% CI 1.28–9.92] for BMI; OR 3.13 [95% CI 1.08–9.09] for %BF; OR 2.80 [95% CI 1.00–7.84] for WHR).

#### Combined Effects of Pregnancy Blood Glucose Level and Maternal Obesity on Offspring Adiposity

Given the known association between maternal pregravid obesity and offspring obesity, we evaluated whether there was a combined effect of two risk factors: high pregnancy blood glucose level (being in the fifth quintile) and maternal pregravid overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) (Supplementary Fig. 1). Having both risk factors increased the risk of girls' adiposity by approximately fourfold, compared with those with neither risk factor. For instance, if a mother had a pregnancy glucose level in the fifth quintile and pregravid BMI  $\geq 25.0$  kg/m<sup>2</sup>, the odds of her daughter being in the BMI category  $\geq 85$ th percentile (OR 3.73 [95% CI 1.89–7.37]), Q4 %BF (OR 3.78 [95% CI 1.87–7.66]), and Q4 WHR (OR 3.93 [95% CI 2.02–7.66]) were substantially higher. Having only a single risk factor did not result in a significant increase in the risk of girls' obesity.

We further tested for an interaction between presence of GDM and pregravid BMI and analyzed the combined effect on girl's adiposity (Table 4). Girls whose mothers had both of these risk factors had the highest odds of having BMI  $\geq 85$ th percentile (OR 5.56 [95% CI 1.70–18.2]), high (Q4) %BF (OR 6.04 [95% CI 1.76–20.7]), and high (Q4) WHR (OR 3.60 [95% CI 1.35–9.58]). Having pregravid BMI  $\geq 25$  absent GDM also increased the risk of girl's obesity, though at much smaller magnitude (60–70% increase compared with referent). Having GDM with normal BMI was not associated with offspring's adiposity, although the sample size was small ( $n = 11$ ), and we had insufficient power to assess these associations.

### Supplemental Analyses

#### Mediation by Birth Weight

To evaluate whether the observed associations were mediated by girl's birth weight, we conducted a secondary analysis including child birth weight. In this population, inclusion of birth weight either as a continuous or categorical variable did not change the effect estimates

**Table 1—Demographic characteristics of the mothers by pregnancy glucose levels: CYGNET Study, 2005–2006**

Glucose	Q1	Q2	Q3	Q4	Q5	P value*
Range (mg/dL)	≤90	91–104	105–119	120–141	>141	
n	84	82	86	84	85	
Age at delivery (years)	32.0 (5.7)	31.4 (6.6)	33.1 (5.9)	33.1 (5.6)	33.5 (5.1)	0.09
Education						0.62
High school or less	12 (16%)	17 (23%)	13 (17%)	16 (21%)	17 (23%)	
Some college	25 (22%)	21 (18%)	20 (17%)	22 (19%)	28 (24%)	
College/university	31 (23%)	29 (22%)	31 (23%)	23 (17%)	20 (15%)	
Postgraduate	15 (17%)	13 (15%)	20 (23%)	22 (25%)	19 (21%)	
Income						0.22
<50,000/year	12 (14%)	23 (27%)	17 (20%)	16 (19%)	16 (19%)	
≥50,000/year	71 (22%)	56 (17%)	67 (20%)	68 (21%)	68 (21%)	
BMI						0.67
Normal (BMI <25 kg/m <sup>2</sup> )	49 (23%)	39 (18%)	49 (23%)	39 (18%)	38 (18%)	
Overweight (25 ≤ BMI < 30 kg/m <sup>2</sup> )	18 (17%)	24 (23%)	20 (19%)	21 (20%)	21 (20%)	
Obese (BMI ≥30 kg/m <sup>2</sup> )	11 (16%)	11 (16%)	13 (19%)	16 (24%)	17 (25%)	
Smoking during pregnancy	4 (20%)	4 (20%)	3 (15%)	3 (15%)	6 (30%)	0.82

Data are N (%) or mean (SD). \*ANOVA for continuous variables and  $\chi^2$  test for categorical variables.

substantially. For the highest quintile of maternal glucose compared with the lowest quintile, the OR for predicting offspring having a BMI >85th percentile was 2.15 (95% CI 1.02–4.52) including birth weight (categorical) did not differ substantially from our prior result (OR 2.28 [95% CI 1.08–4.84]). This suggests that birth weight does not fully mediate

the association between maternal glucose levels and offspring adiposity.

### CONCLUSIONS

In our multiethnic group of mother-daughter pairs, we observed that maternal pregnancy hyperglycemia, whether just below the diagnostic threshold of GDM or as GDM, were

both associated with increased risk of childhood obesity, findings that held independent of maternal age at delivery, race/ethnicity, pregravid BMI, girls' age, and age at onset of puberty. In addition, we found that the risk of childhood obesity was highest among offspring of mothers with GDM and pregravid obesity.

**Table 2—Baseline characteristics of the girls by maternal pregnancy glucose levels, CYGNET Study, 2005–2006**

Glucose	Q1	Q2	Q3	Q4	Q5	P value*
Range (mg/dL)	≤90	91–104	105–119	120–141	>141	
N	84	82	86	84	85	
Age (years)						0.64
6	19 (19%)	22 (22%)	16 (16%)	21 (21%)	21 (21%)	
7	62 (20%)	59 (19%)	70 (22%)	62 (20%)	63 (20%)	
8	3 (50%)	1 (17%)	0 (0%)	1 (17%)	1 (17%)	
Race/ethnicity						0.13
White	41 (23%)	35 (19%)	35 (19%)	37 (20%)	33 (18%)	
Asian	6 (12%)	9 (17%)	14 (27%)	10 (19%)	13 (25%)	
Latina	12 (12%)	19 (19%)	19 (19%)	24 (24%)	27 (27%)	
African American	25 (29%)	19 (22%)	18 (21%)	13 (15%)	12 (14%)	
Tanner stage						0.79
Breast ≥2	6 (20%)	5 (17%)	7 (23%)	8 (27%)	4 (13%)	
Pubic hair ≥2	7 (23%)	8 (26%)	6 (19%)	6 (19%)	4 (13%)	0.83
BMI						0.26
Normal (BMI <85th percentile)	67 (22%)	56 (19%)	58 (19%)	64 (21%)	56 (19%)	
Overweight (85th ≤ BMI < 95th)	8 (13%)	11 (18%)	17 (28%)	12 (20%)	12 (20%)	
Obese (BMI ≥95th)	9 (15%)	15 (25%)	11 (18%)	8 (13%)	17 (28%)	
%BF	17.9 (8.2)	19.2 (8.9)	19.1 (8.3)	18.9 (8.7)	20.5 (10.0)	0.46
WHR	0.48 (0.047)	0.49 (0.057)	0.49 (0.05)	0.48 (0.048)	0.50 (0.059)	0.08
Total energy intake (kcal/day)	1,623 (275)	1,572 (322)	1,627 (468)	1,533 (308)	1,493 (313)	0.05
Total fat intake (g/day)	58.3 (13.9)	53.0 (12.6)	55.6 (18.9)	52.5 (14.4)	51.5 (14.4)	0.03
Physical activity: LN METs	1.9 (1.3)	1.9 (1.3)	1.9 (1.3)	1.8 (1.3)	1.6 (1.4)	0.68
Birth weight (g)	3,305 (499)	3,350 (560)	3,425 (528)	3,430 (532)	3,346 (695)	0.54
Gestational age at birth (weeks)	39.3 (1.9)	39.5 (2.0)	39.4 (1.6)	39.1 (1.6)	38.6 (2.6)	0.06

Data are N (%) or mean (SD). LN, natural log; MET, metabolic equivalent. \*ANOVA for continuous variables and  $\chi^2$  test for categorical variables.

**Table 3—Associations between maternal pregnancy glucose levels and offspring girls' BMI, %BF, and WHR: CYGNET Study, 2005–2012\***

Quintile of maternal glucose (mg/dL)	Offspring adiposity measures								
	BMI ≥85th percentile			Q4 %BF			Q4 WHR		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
Q1: <90	75	1.00	Reference	71	1.00	Reference	75	1.00	Reference
Q2: 91–104	73	1.85	0.86 3.97	62	1.35	0.60 3.05	73	1.68	0.77 3.65
Q3: 105–119	76	2.08	0.97 4.46	65	2.18	0.99 4.79	76	1.76	0.82 3.79
Q4: 120–141	74	1.26	0.55 2.89	67	1.66	0.76 3.60	74	1.22	0.54 2.77
Q5: >141	72	2.28	1.08 4.84	63	2.51	1.16 5.40	72	2.48	1.17 5.22
Test for trend (P value)		0.13			0.03			0.07	
Q5: without GDM	49	1.81	0.79 4.15	46	1.88	0.80 4.42	49	2.11	0.93 4.78
Q5: with GDM	19	3.56	1.28 9.92	13	3.13	1.08 9.09	19	2.80	1.00 7.84

\*Generalized estimating equation models adjusted for race/ethnicity, maternal pregravid BMI, girls' age, Tanner stages, and maternal age at delivery.

To our knowledge, this is one of the first studies to examine the effect of pregnancy hyperglycemia and GDM on offspring's adiposity beyond the measure of general obesity (using the proxy BMI), adjusting for maternal pregravid BMI. This finding corroborates previous well-designed studies suggesting that exposure to maternal GDM or type 2 diabetes in utero may increase the risk of offspring adiposity in a large group ( $n > 7,000$ ) of German children (29), in multiethnic children age 6–13 in Colorado (10), and among younger children in eastern Massachusetts (30). In these latter studies, exposure to maternal GDM was associated with higher waist circumference (10) and adiposity (30) (measured by skinfold thickness), but not BMI after adjustment for important covariates including maternal pregravid BMI. Our results corroborate this finding as the dose-effect associations between pregnancy glucose levels and adiposity outcomes were stronger for percent fat and WHR than BMI (Table 3). %BF and abdominal (visceral) obesity are better predictors of adult chronic conditions such as insulin resistance, metabolic syndrome, type 2 diabetes, and cardiovascular disease than BMI (20,21,31).

Our results thus suggest that exposure to hyperglycemia or GDM in utero increases the risk of metabolic dysregulation in the offspring, manifested as greater adiposity.

Second, most prior studies evaluated the association of childhood obesity with diagnosed or self-reported GDM or type 2 diabetes (10–16), and little is known regarding the effect of maternal pregnancy glucose levels below the diagnostic threshold of GDM. Our results indicate that pregnancy glucose levels  $>140$  mg/dL in the screening test, which coincides with the cutoff point for the diagnostic test for GDM ( $\geq 140$  mg/dL), is significantly associated with adiposity of offspring girls. Among the women in the highest quintile, only one-third ( $n = 26$ ) met the criteria of GDM. While elevated maternal glucose levels without GDM carried an increased risk of offspring adiposity, our supplemental analyses comparing the results between women with and without GDM demonstrated that the associations were consistently stronger among women with GDM (Table 3). Furthermore, we also found that female offspring of women with pregravid obesity and GDM had three to six times higher risk of obesity

compared with the referent without either of the risk factors. This finding highlights the importance of identifying these high-risk women and intervening with treatment and lifestyle modification. During the pregnancy “teachable moment,” GDM or overweight women may be alerted to the increased risk of their offspring being overweight, which could potentially encourage the adoption of preventive behaviors, leading to upstream intervention of childhood obesity.

Lastly, we found that the association between maternal pregnancy glucose and offspring adiposity was not mediated by birth weight. This results supports the findings from long-term Pima Indian study (32) and suggests that the long-term consequences of fetal overnutrition are not fully explained by increased fetal growth. Similarly, adjustment for girls' diet (total fat and energy intake) or physical activity did not change the associations (data not shown). Exposure to high levels of glucose in utero, therefore may predispose the offspring to altered metabolic patterns, affecting long-term regulation of energy balance. These exposures may influence the development of hypothalamic

**Table 4—Association of maternal GDM and pregravid BMI on offspring adiposity, CYGNET Study, 2005–2012**

	BMI ≥85th percentile			Q4 %BF			Q4 WHR		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
BMI <25 and no GDM	202	1.0	Reference	178	1.0	Reference	202	1.0	Reference
BMI <25 and GDM	11	0.58	0.15 2.27	7	0.39	0.08 1.99	11	1.40	0.43 4.60
BMI ≥25 and no GDM	159	1.71	1.08 2.72	144	1.59	1.00 2.55	159	1.78	1.09 2.91
BMI ≥25 and GDM	11	5.56	1.70 18.2	9	6.04	1.76 20.7	11	3.60	1.35 9.58
P value for interaction		0.03			0.01			0.01	

circuits that regulate body weight, as well as endocrine pancreatic function, changes in the proportion of lean versus fat body mass, and other cycles of metabolic programming (33).

While our findings represent important additions to the evidence base, they should be interpreted with caution. First, maternal pregravid weight and height were self-reported. However, because of the unique availability of the linkage of child medical records to maternal records at KPNC, we were able to compare the self-reported data with those using measured height and weight during the pregnancy in the electronic medical record (measured at alpha fetoprotein test). The results were similar (data not shown), making it unlikely that self-report per se biased the results. Second, since this is an observational study, we cannot preclude potential confounding by unmeasured factors that could explain the observed association. The availability of lifestyle, demographic, and clinical data, such as girls' diet, physical activity, Tanner stage, and maternal pregravid BMI, collected in-person from the study enabled us to investigate the effect of maternal glucose levels independent of these factors on offspring adiposity. However, these factors are not measured with complete accuracy, and it is possible that there are other unmeasured psychosocial, genetic, and environmental factors that may explain some of the association. Lastly, only girls were included in this study. It is possible that there is effect modification by sex in the observed associations.

In conclusion, in this ethnically diverse sample of mother-daughter pairs, subclinical hyperglycemia and GDM were both found to be important predictors of offspring adiposity in girls, independent of maternal pregravid obesity. The concept of windows of susceptibility over the life course provides an important conceptual framework for understanding how prenatal exposures may influence the health of offspring and the cycle may continue over generations. Our study suggests that exposures during the intrauterine period affect the offspring's obesity trajectory, which will subsequently shape health outcomes of the girls later in life. Because of this, as Gillman and Ludwig (7) state in a recent perspective article,

it is imperative that research on childhood obesity move more upstream, focusing on pregnant women or even women who are planning on becoming pregnant in order to improve lifelong health trajectories of the women and the offspring. Ongoing intervention studies targeting pregnant or preconceptual women (34) have promising clinical and public health implications to slow the ever-increasing rate of obesity and diabetes in the U.S.

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