Children Exposed to Maternal Obesity or Gestational Diabetes Mellitus During Early Fetal Development Have Hypothalamic Alterations That Predict Future Weight Gain

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OBJECTIVE

Exposure in utero to maternal obesity or gestational diabetes mellitus (GDM) is linked to a high risk for obesity in offspring. Animal studies suggest that these exposures disrupt the development of the hypothalamus, a brain region that regulates body weight, predisposing offspring to develop obesity. This study tested the hypothesis in humans that in utero exposure to maternal obesity and/or GDM is associated with alterations in the hypothalamic response to glucose and the altered hypothalamic response would predict greater increases in child adiposity 1 year later.

RESEARCH DESIGN AND METHODS

Participants were 91 children aged 7–11 years with and without in utero exposure to GDM. Maternal prepregnancy BMI and GDM exposures were determined from electronic medical records. Arterial spin labeling MRI was used to determine the child's hypothalamic blood flow response to oral glucose. Anthropometric measures were acquired in all children at their initial visit and again 1 year later in a subset of 44 children.

RESULTS

Children exposed to GDM diagnosed at ≤26 weeks' gestation had increased hypothalamic blood flow (a marker of hypothalamic activation) in response to glucose when compared with unexposed children, and results remained after adjustments for child age, sex, BMI, and maternal prepregnancy BMI. Maternal prepregnancy BMI was positively associated with the child's hypothalamic response to glucose. Greater hypothalamic response to glucose predicted greater increases in child's BMI 1 year later.

CONCLUSIONS

Increased glucose-linked hypothalamic activation during childhood represents a possible mechanism by which exposure to maternal metabolic disorders during fetal development increases future risk for obesity.

Global rates of childhood obesity have increased dramatically. Evidence suggests that exposure in utero to maternal obesity or gestational diabetes mellitus (GDM) may contribute to these alarming trends (1–5). Children born to mothers with GDM or obesity during pregnancy have an increased likelihood of developing obesity and metabolic disorders compared with unexposed children (1–5). Studies in siblings discordant for maternal exposures suggest that the risk is in excess of

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that attributable to genetics and shared environment (1,2,6,7). Although the biological underpinnings of such maternal–fetal programming are not completely understood, compelling studies in animal models suggest that in utero exposure to maternal obesity or diabetes leads to alterations in the development and function of the hypothalamus, predisposing offspring to develop obesity (8–12). To date, no studies have investigated whether in utero exposure to maternal obesity or GDM is associated with changes in hypothalamic function in humans.

Previous functional MRI studies in adults have shown that obesity is associated with attenuation of the normal reduction in hypothalamic activity that follows ingestion of glucose (13,14). A study in adolescents showed that obesity was associated with an increase in hypothalamic blood flow (BF) (a marker of activation) in response to glucose that was not observed in lean adolescents (15). Taken together, these results suggest that an alteration in the hypothalamic response to oral glucose may be a marker of risk for obesity. The current study aimed to determine the impact of in utero exposure to maternal obesity and GDM on glucose-linked changes in cerebral BF (CBF) in the hypothalamus, the key brain region for body weight regulation and the region where maternal–fetal programming effects were shown to occur in animal models. In addition, we examined whether an alteration in the hypothalamic response to glucose in children would predict greater increases in adiposity 1 year later. We hypothesized that children exposed in utero to maternal obesity or GDM would have an increased hypothalamic BF response to oral glucose, which would predict greater future increases in adiposity.

RESEARCH DESIGN AND METHODS

Participants

Participants of the Brain Child Study were aged 7–11 years and born at a Kaiser Permanente Southern California (KPSC) hospital with documented exposure to maternal GDM or normal glucose levels during pregnancy. Children were excluded if they had a history of premature birth (<37 weeks' gestation), had medical or psychiatric disorders, used medications known to alter metabolism, had contraindications to MRI, or were left-handed. Institutional review boards at the University of Southern California (USC) (#HS-14–00034) and KPSC (#10282) approved this study. Participants' parents gave written informed consent, and children provided written informed assent. Potential participants were identified through the KPSC electronic medical record (EMR) and contacted to confirm eligibility and determine willingness to participate. Maternal pre-existing diabetes was excluded by ICD-9-Clinical Modification diagnosis code 250 and/or use of antidiabetes medications outside of pregnancy prior to this pregnancy. Household income at birth was estimated based on census tract of residence. Maternal education at birth was extracted from birth certificates in EMR. GDM-exposed children were identified first followed by unexposed controls, with a goal of minimizing unbalance between groups in the distribution of age, sex, ethnicity, and maternal prepregnancy BMI category based on Centers for Disease Control and Prevention definitions (16).

Assessment of Exposure to Maternal GDM, Prepregnancy Obesity, and Maternal Weight Gain During Pregnancy

Diagnosis of maternal GDM was based on one of two sets of plasma glucose (PG) values measured in a KPSC clinical laboratory: *1*) PG level ≥200 mg/dL 1 h after a 50-g glucose challenge, or *2*) at least two PG values meeting or exceeding the following values on the 100-g or 75-g oral glucose tolerance test: fasting, 95 mg/dL; 1 h, 180 mg/dL; 2 h, 155 mg/dL; and 3 h, 140 mg/dL. Maternal prepregnancy BMI was calculated using maternal height and weight from the EMR on the date closest to last menstrual period. Gestational weight gain over the entire pregnancy was determined by maternal body weight data recorded in the EMR. Gestational age at GDM diagnosis was calculated using the date of the first glucose test results that were diagnostic of GDM, date of delivery, and gestational age at delivery, all of which were obtained from the EMR. PG levels 1 h after the 50-g glucose challenge during pregnancy were also obtained from the EMR.

In-Person Visits

The study included two baseline visits and a 1-year follow-up visit. The follow-up visit was added to the study protocol ~1 year after the original study began, resulting in a subset of children who returned for follow-up. The visits were conducted after an overnight fast. Visit 1 occurred at the Clinical Research Unit of the USC Diabetes and Obesity Research Institute. Height was measured to the nearest 0.1 cm using a stadiometer and weight to the nearest 0.1 kg using a calibrated digital scale. BMI was calculated as weight in kilograms divided by height in meters squared. BMI percentiles and BMI *z* scores were determined based on Centers for Disease Control and Prevention standards. Waist and hip circumferences were measured in triplicate to the nearest 0.1 cm. Waist circumference was measured at the midpoint between the iliac crest and lower costal margin in the midaxillary line. Hip circumference was measured around the maximum circumference of the buttocks. Percent body fat was measured by a trained staff member using bioelectrical impedance (Tanita Corporation of America, Inc.). Tanner stage was assessed by physical examination and/or by a validated sex-specific assessment questionnaire for children and parents (17–19). The correlation coefficient between Tanner staging assessed by physical examination and by questionnaire was 0.85.

Visit 2 occurred at the USC Dana and David Dornsife Cognitive Neuroimaging Center. Participants lay supine inside the bore of a MAGNETOM Prisma^{fit} 3T MRI scanner. After initial localizers, a baseline pulsed arterial spin labeling (PASL) scan was acquired followed by a high-resolution anatomical scan. Children then ingested a standardized glucose drink used for glucose tolerance testing (1.75 g/kg body weight, maximum 75 g) (Azer Scientific) within 2 min and returned to the scanner for another PASL scan, which began 10 min after completion of glucose ingestion. The timing of PASL acquisitions is based on prior work showing that the maximum response to glucose occurs ~15 min after glucose ingestion (13,14,20,21). Mock scanner training was performed prior to the actual scan to familiarize children with the MRI procedures. The 1-year follow-up visit occurred at the Clinical Research Unit. Procedures for anthropometric measurements were identical to those performed at baseline visit 1.

MRI Methods

The PASL sequence used the QUIPSS-II method (22). A proximal inversion with

a control for off-resonance effects mode was used to provide high labeling efficiency (23). The PASL sequence was acquired along with one M0 image with the following parameters: field of view, 192 mm; matrix, 64 × 64; bandwidth, 2,232 Hz/pixel; slice thickness, 5 mm; interslice spacing, 0 mm; repetition time, 4,000 ms; echo time, 30 ms; flip angle, 90°; timing of the inversion pulses (TI) TI1/TIs/TI2, 700/1,800/1,800 ms; label duration, 1,675 ms; slab thickness, 100 mm; and in-plane resolution, 3 × 3 mm^2. The TI was optimized to reduce intravascular signal intensity at 3T (24). The duration of the PASL acquisition was 5 min and 14 s. A 4-min high-resolution 3D Magnetization Prepared Rapid Gradient Echo sequence was used to acquire structural images for multisubject registration with the following parameters: repetition time, 2,530 ms; echo time, 2.62 ms; bandwidth, 240 Hz/pixel; flip angle, 9°; slice thickness, 1 mm; field of view, 256 × 256 mm; matrix, 256 × 256; and voxel resolution, 1 × 1 × 1 mm.

The Bayesian Inference for Arterial Spin Labeling toolbox was used to determine regional BF within the hypothalamus. PASL data were motion corrected and then tagged, and untagged images were subtracted to obtain perfusion-weighted images (25). PASL volumes were registered to the individual participant's T1-weighted high-resolution anatomical volume using an affine registration with 12 df. Regional BF in the hypothalamus was calculated from the PASL acquisition obtained before glucose ingestion and again from the PASL acquisition obtained after glucose ingestion. Mean CBF across the whole brain was also calculated before and after glucose ingestion.

The bilateral hypothalamic region of interest (ROI) (Fig. 1*C*) was defined by drawing a 2-mm radius around the peak voxel reported in Page et al. (26), where the hypothalamus showed a response to changes in circulating glucose levels. While our hypothalamus ROI was made based on an adult study, the coordinates we used overlapped with those reported in a pediatric study of the hypothalamic response to oral glucose (15). The hypothalamus ROI in standard Montreal Neurological Institute space was inverse transformed to each individual's T1-weighted high-resolution image. Visual inspection was performed in each individual's hypothalamus ROI, and the ROI was manually edited to ensure it was constrained within the hypothalamus. In three participants, the hypothalamus ROI was manually edited due to several voxels misaligned to nearby regions.

Statistical Analyses

Maternal and child characteristics were compared between GDM-exposed and unexposed groups by *t* tests for continuous variables and χ^2 tests for categorical variables. Hypothalamic response to glucose was calculated as the difference in hypothalamic BF corrected for whole-brain CBF during glucose ingestion test (hypothalamic BF/whole-brain CBF after glucose ingestion − hypothalamic BF/whole-brain CBF before glucose ingestion). This approach corrected for both basal hypothalamic BF and whole-brain CBF values. Relationships between hypothalamic responses and intrauterine exposures to maternal GDM and/or obesity were assessed using linear regression in which prepregnancy BMI was modeled as a continuous variable and GDM exposure was modeled as a categorical variable in two different ways: *1*) exposure to GDM diagnosed at any time during pregnancy versus no exposure, and *2*) exposure to GDM diagnosed at ≤26 weeks' gestation versus GDM diagnosed at >26 weeks versus no exposure. These temporal cutoffs were based predominantly on prior work showing that diagnosis of GDM by 26 weeks' gestation is associated with a greater risk of neurodevelopmental disorders compared with later diagnosis or no GDM (27). We also treated gestational age at diagnosis of GDM as a continuous variable and assessed timing of exposure in association with hypothalamic responses among children exposed to GDM. Regression analyses were performed without and with adjustment for the child's age, sex, and BMI *z* score and additional adjustments for the other maternal exposure variables. To control for potential confounding due to socioeconomic status, further adjustments for household income and maternal education at birth were performed. Because 93% of children were Tanner stage 1, Tanner stage was not adjusted in the regression models.

The relationships between childhood adiposity measures and exposure to maternal GDM and/or maternal obesity were assessed using a linear regression approach analogous to the one outlined above. Relationships between hypothalamic response to glucose and childhood adiposity at baseline and change in childhood adiposity at 1-year follow-up were also examined using the linear regression approach. All analyses were performed using SAS Enterprise Guide 9.4 (SAS Institute, Cary, NC) and R 3.4.4 (64 bit). All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.

RESULTS

Participants

Ninety-seven children met the inclusion criteria. Six children were excluded from MRI analyses (four for excessive motion, one for incidental findings on MRI, and one for not completing the MRI), leaving a total of 91 children (53 GDM-exposed and 38 unexposed) for the analyses. The mean ± SD age at the baseline visit was 8.4 ± 0.9 years; 93% of the children were Tanner stage 1, and 60% were female. There were no significant differences in age, race/ethnicity, pubertal status, maternal prepregnancy BMI, income at birth, or maternal education between GDM-exposed and unexposed groups. Maternal prepregnancy BMI ranged between 19.0 and 50.4 kg/m^2 (Table 1). Within the GDM-exposed group, 15 children were exposed to GDM diagnosed ≤26 weeks' gestation, and 38 children were exposed to GDM diagnosed >26 weeks' gestation. Mean hypothalamic BF was 25.42 ± 9.66 mL/100 g/min before and 27.61 ± 10.21 mL/100 g/min after glucose. Mean whole-brain CBF was 29.75 ± 5.57 mL/100 g/min before and 32.75 ± 6.17 mL/100 g/min after glucose. The median gestational age of diagnosis for those with GDM diagnosed ≤26 weeks' gestation was 11.0 (interquartile range 7.3, 17.6) weeks, whereas the median gestational age of diagnosis for those with GDM diagnosed >26 weeks' gestation was 29.3 (interquartile range 28, 30.6) weeks. Mean ± SD PG levels 1 h after the 50-g glucose challenge during pregnancy were significantly greater in the subgroup of GDM diagnosed ≤26 weeks' gestation (178 ± 37 mg/dL) compared with the subgroup of GDM diagnosed >26 weeks' gestation (145 ± 40 mg/dL; $P = 0.02$) and the unexposed group (115 ± 23 mg/dL; $P < 0.001$).

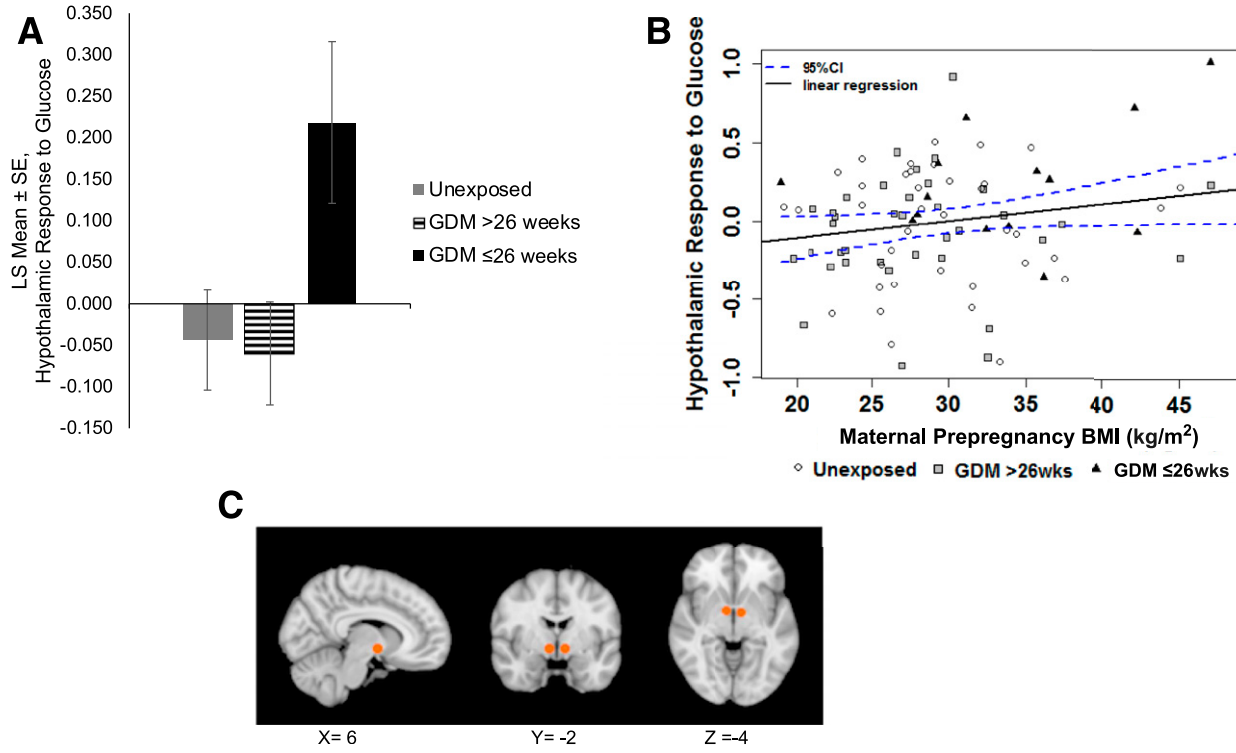

Figure 1—*A*: Least square (LS) mean ± SE of child hypothalamic response adjusted for child age, sex, BMI *z* score, and maternal prepregnancy BMI by GDM exposure categories of unexposed (gray bar), GDM diagnosed at >26 weeks' gestation (black striped bar), and GDM diagnosed at ≤26 weeks' gestation (black bar). *B*: Child age, sex, and BMI *z* score adjusted residuals of hypothalamic response to glucose by maternal prepregnancy BMI. Unexposed children indicated by white circles, GDM diagnosed >26 weeks (wks) by gray squares, and GDM diagnosed ≤26 weeks by black triangles. *C*: Representative figure showing the hypothalamic ROI in sagittal, coronal, and axial planes. X, Y, and Z refer to Montreal Neurological Institute atlas coordinates.

Maternal GDM and Child's Hypothalamic Responses to Glucose

Children exposed to GDM at any time during pregnancy and unexposed children had similar hypothalamic responses to glucose (mean ± SE 0.01 ± 0.38 vs. −0.05 ± 0.38, respectively; P = 0.50, unadjusted). When gestational age at diagnosis of GDM was treated as a continuous variable, there was a negative association with hypothalamic response to glucose (correlation coefficient = −0.27; P = 0.05, unadjusted), suggesting that earlier gestational age at diagnosis of GDM was associated with an increase in children's hypothalamic response to glucose. When gestational age at diagnosis of GDM was divided at 26 weeks, children exposed to GDM after this time had similar mean hypothalamic responses to glucose as unexposed children (−0.07 ± 0.37 vs. −0.05 ± 0.38, respectively; P = 0.76, unadjusted). However, the hypothalamic response in children exposed to GDM by 26 weeks' gestation was 0.21 ± 0.36, which was significantly higher than each of the other two groups (P = 0.01 compared with GDM >26 weeks and P = 0.03 compared with unexposed). Hypothalamic responses remained higher in the group exposed to GDM by 26 weeks after adjusting for child age and sex (β = 0.262 ± 0.115; P = 0.03) (Table 2). Adjustment for child BMI *z* score had almost no effect on the association (β = 0.259 ± 0.117; P = 0.03) (Table 2). Further adjusting for maternal prepregnancy BMI had a small effect (β = 0.233 ± 0.119; P = 0.06) (Table 2), and further adjusting for socioeconomic status did not affect the findings (P = 0.06) (Table 2). Figure 1*A* depicts the child age, sex, BMI *z* score, and maternal prepregnancy BMI adjusted means by the maternal GDM status. Adjustment for glucose levels from the 50-g glucose challenge test eliminated the significant association for the early GDM group (β = 0.058 ± 0.159; P = 0.72), suggesting that severity of GDM plays a role explaining the association.

Maternal Obesity and Child's Hypothalamic Response to Glucose

Maternal prepregnancy BMI was positively associated with child's hypothalamic responses to glucose (β = 0.061 ± 0.028 for every 5-unit increase in maternal prepregnancy BMI; P = 0.03, unadjusted) (Table 2). This association was independent of child age, sex, and BMI *z* score (β = 0.060 ± 0.030; P = 0.05) (Table 2 and Fig. 1*B*). Further adjusting for maternal gestational weight gain slightly attenuated the association (β = 0.054 ± 0.34; P = 0.11). Additional adjustment for GDM exposure (GDM diagnosis ≤26 or >26 weeks) attenuated the association (β = 0.043 ± 0.31; P = 0.17) (Table 2) such that it was no longer significant, suggesting that part of the association with prepregnancy BMI was mediated by early diagnosis of GDM. Further adjusting for socioeconomic status had no effect on the findings (Table 2). Gestational weight gain was not significantly associated with hypothalamic response (correlation coefficient = −0.13; P = 0.21).

Effect of Maternal GDM and Maternal Obesity on Child's Adiposity at Baseline

Of the seven child adiposity measures assessed, only waist-to-hip ratio and waist-to-height ratio differed between GDM-exposed and unexposed groups

Table 1—Subject characteristics*

Characteristic	Overall	GDM (*N* = 53)	Unexposed (*N* = 38)	*P* value
Child				
Age (years)	8.4 (0.9)	8.3 (0.7)	8.5 (1.0)	0.28
Sex				0.13
Female	55 (60.4)	36 (67.9)	19 (50.0)	
Male	36 (39.6)	17 (32.1)	19 (50.0)	
BMI (kg/m^2)	18.8 (4.0)	19.3 (4.5)	18.1 (3.1)	0.19
BMI *z* score	0.75 (1.09)	0.85 (1.13)	0.62 (1.04)	0.32
Total body fat (%)	25.1 (8.7)	26.1 (9.6)	23.6 (7.2)	0.19
Waist circumference (cm)	63.7 (11.0)	65.3 (12.3)	61.5 (8.6)	0.11
Hip circumference (cm)	72.8 (8.9)	73.4 (10.2)	71.9 (6.8)	0.43
Height (cm)	131.4 (7.8)	131.3 (7.4)	131.5 (8.3)	0.94
Waist-to-height ratio	0.48 (0.07)	0.50 (0.08)	0.47 (0.06)	0.02
Maternal				
Prepregnancy BMI (kg/m^2)	30.0 (7.0)	30.3 (7.8)	29.5 (5.7)	0.59
Prepregnancy weight category				0.76
Normal weight (BMI $<$25 kg/m^2)	20 (22.0)	13 (24.5)	7 (18.4)	
Overweight (BMI $\geq$25 and $<$30 kg/m^2)	35 (38.5)	19 (35.8)	16 (42.1)	
Obese (BMI $>$30 kg/m^2)	36 (39.6)	21 (39.6)	15 (39.5)	
Race/ethnicity				0.19
Hispanic	48 (52.8)	30 (56.6)	18 (47.4)	
Non-Hispanic black	13 (14.3)	5 (9.4)	8 (21.1)	
Non-Hispanic white	20 (22.0)	10 (18.9)	10 (26.3)	
Other	10 (11.0)	8 (15.1)	2 (5.3)	
Income group at birth ($)				0.23
$<$30,000	11 (12.4)	4 (7.6)	7 (19.4)	
30,000–50,000	24 (27.0)	14 (26.4)	10 (27.8)	
50,000–70,000	28 (31.5)	21 (39.6)	7 (19.4)	
70,000–90,000	13 (14.6)	7 (13.2)	6 (16.7)	
$\geq$90,000	13 (14.6)	7 (13.2)	6 (16.7)	
Maternal education				0.72
High school or less	18 (20.2)	12 (22.6)	6 (16.7)	
Some college	26 (29.2)	16 (30.2)	10 (27.8)	
College and postgraduate	45 (50.6)	25 (47.2)	20 (55.6)	

Data are mean (SD) or *N* (%). *For continuous variables, *P* value is calculated from *t* test; for categorical variables, *P* value is calculated using Fisher exact test. One unexposed child did not undergo body fat measurement, leaving *N* = 90 for analysis. Two unexposed children were missing income and education variables.

(Table 1). Regression analysis revealed similar associations between GDM exposure and child adiposity measures in subgroups exposed to GDM diagnosed $\leq$26 weeks' and $>$26 weeks' gestation (Supplementary Table 1). All seven variables of child adiposity were positively associated with maternal prepregnancy BMI and remained significant after adjusting for child age and sex and maternal GDM status (Supplementary Table 2).

Table 2—Relationship of exposure to maternal GDM after 26 weeks' gestation, GDM diagnosed before 26 weeks' gestation, and maternal prepregnancy BMI to child's hypothalamic response to glucose

	GDM $>$26 weeks vs. unexposed		GDM $\leq$26 weeks vs. unexposed		Prepregnancy BMI	
Model	β (SE)*	*P* value	β (SE)*	*P* value	β (SE)*	*P* value
Model 1	−0.026 (0.085)	0.76	0.261 (0.113)	0.02	0.061 (0.028)	0.03
Model 2	−0.016 (0.087)	0.85	0.262 (0.115)	0.03	0.059 (0.029)	0.04
Model 3	−0.017 (0.087)	0.84	0.259 (0.117)	0.03	0.060 (0.030)	0.05
Model 4	−0.008 (0.087)	0.93	0.223 (0.119)	0.06	0.043 (0.031)	0.17
Model 5	−0.036 (0.089)	0.69	0.227 (0.121)	0.06	0.050 (0.032)	0.12

Model 1: unadjusted. Model 2: adjusted for child age and sex. Model 3: adjusted for child age, sex, and BMI *z* score. Model 4: adjusted for child age, sex, and BMI *z* score + maternal prepregnancy BMI (for GDM exposures) or maternal GDM status as a three-categorical variable (for prepregnancy BMI). Model 5: adjusted for child age, sex, and BMI *z* score + maternal prepregnancy BMI or maternal GDM status as a three-categorical variable + income at birth + maternal education at birth. *Regression coefficient (SE) from linear regression models.

Child Adiposity Measures at 1-Year Follow-up

Forty-four children (27 GDM-exposed and 17 unexposed) returned for the 1-year follow-up visit. There was no difference in demographics or anthropometrics in the children who returned for follow-up and those who did not (Supplementary Table 3). At follow-up, children had significant increases in BMI (0.71 ± 1 kg/m^2; $P < 0.001$), total body fat (0.85 ± 2.4%; $P = 0.02$), waist circumference (3.5 ± 4.2 cm; $P < 0.001$), and hip circumference (3.3 ± 3.4 cm; $P < 0.001$), whereas BMI *z* scores, waist-to-hip ratio, and waist-to-height ratios were not changed at 1-year follow-up compared with baseline (Supplementary Table 4).

Child's Hypothalamic Response to Glucose, Maternal GDM and Obesity, and Changes in Child's Adiposity Measures 1 Year Later

Although no significant associations were observed between hypothalamic responses to glucose and measures of child adiposity at baseline (correlation coefficients ranged from 0.05 to 0.07; $P > 0.50$), greater hypothalamic response to glucose at baseline was associated with greater increases in child's BMI 1 year later ($\beta = 0.891$ kg/m^2 increase in child BMI per 1-unit increase in hypothalamic response to glucose; $P = 0.02$ after adjusting for child's baseline BMI, age, and sex) (Fig. 2 and Supplementary Table 5). Greater maternal prepregnancy BMI was also significantly associated with greater increase in child's BMI ($\beta = 0.297$ kg/m^2 increase in child BMI per 5 kg/m^2 higher in maternal prepregnancy BMI; $P = 0.03$). Maternal GDM status was not associated with the child's increase in BMI ($P = 0.48$). Multivariate analysis with hypothalamic response to glucose and maternal prepregnancy BMI together as independent variables in one model attenuated the associations for each such that the β was reduced from 0.891 to 0.719 (a 20% drop) for hypothalamic response to glucose, and the β was reduced from 0.297 to 0.224 (a 25% drop) for maternal prepregnancy BMI (Supplementary Table 5), suggesting that hypothalamic response to glucose may partially mediate the association between exposure to maternal obesity and child's BMI increase 1 year later.

CONCLUSIONS

Our results demonstrate that, independent of children's current BMI, there are significant associations between in utero exposure to maternal obesity or GDM diagnosed by 26 weeks' gestation and increases in hypothalamic responses to glucose at 7–11 years of age. Moreover, the increased hypothalamic response to glucose was predictive of greater increases in child's adiposity 1 year later. Maternal obesity was associated with child's adiposity at 7–11 years of age and with increases in adiposity 1 year later. Part of this association was explained by hypothalamic responses to glucose at 7–11 years of age. Thus, the observed increases in the children's hypothalamic response to glucose represent a possible mechanism by which exposure to maternal metabolic disorders during fetal development increases the risk for obesity later in life.

The Developmental Origins of Health and Disease hypothesis states that the nutritional and metabolic environment encountered in utero programs one's risk for disease in adult life (28). Cohort studies have supported this hypothesis by showing significant relationships between maternal obesity and diabetes during pregnancy and increased risk for obesity and metabolic disorders in the offspring (1,2,4,5). Experimental studies in animal models provide compelling evidence that intrauterine exposure to maternal obesity and/or diabetes results in alterations in the development and function of the hypothalamus predisposing to future obesity (8–12).

Sophisticated neuroimaging technology facilitates the translation of these important animal findings into humans. Studies have shown that maternal GDM (29) and insulin resistance (30) were associated with slower fetal brain responses to an auditory stimulus, and exposure to maternal obesity during pregnancy was negatively associated with brain white matter development in infants (31). The present report further supports the concept that in utero exposure to GDM or maternal obesity in humans can alter early brain development. We provide novel information about the impact of such exposure on glucose-linked activation in the hypothalamus, the key brain region for body weight regulation, and the region where maternal–fetal programming effects were shown to occur in animal models. To study the hypothalamic functional response to glucose, we used PASL, a noninvasive way to measure CBF that uses magnetically labeled arterial blood water as an endogenous tracer. Similar to positron emission tomography, PASL allows the quantification of CBF in physiological units (mL of blood/100 g of tissue/min), providing an important physiological parameter for the evaluation of brain function. PASL has been used to examine hypothalamic responses to changes in circulating glucose levels in both adults and children and provides reproducible and reliable global and regional CBF measurements (15,20,21,26). Pediatric perfusion images provide a stronger perfusion signal and better delineation of brain regions when compared with adult perfusion images, suggesting that PASL methods may be particularly rigorous for examining brain function in children (32).

Numerous studies have used functional MRI to examine the hypothalamic response to a standardized oral glucose load in adults (13,14,20,21,33,34). PASL studies in healthy-weight adults reported reductions in hypothalamic BF in response to glucose relative to baseline (20,21). While the magnitude of the hypothalamic BF response to glucose was similar in healthy-weight adults and children, the response was in the opposite direction and significantly increased among children exposed versus unexposed to maternal obesity or early diagnosed GDM. Notably, a study in

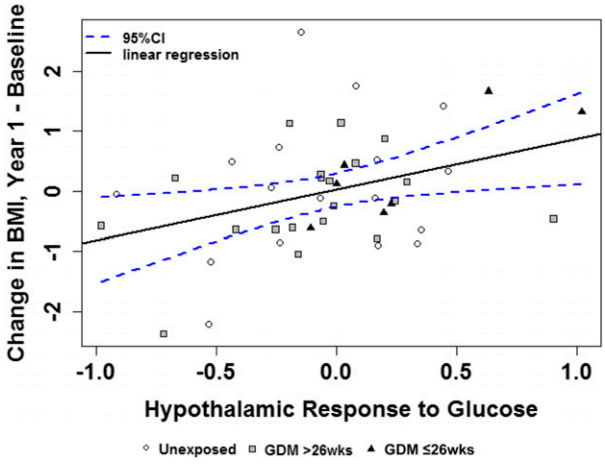

Figure 2—Child age, sex, and baseline BMI adjusted residuals of the change in BMI by hypothalamic response to glucose. Unexposed children indicated by white circles, GDM diagnosed >26 weeks (wks) by gray squares, and GDM diagnosed ≤26 weeks by black triangles.

adolescents showed that obese, but not lean, adolescents had increased hypothalamic BF in response to glucose (15). Our finding that exposure to maternal GDM or obesity is associated with altered hypothalamic responses in children that are directionally similar to alterations seen in obese adolescents provides evidence that early life programming may contribute to the development of obesity. Importantly, the impact of early exposure to GDM or maternal obesity on hypothalamic responses was independent of children's current BMI, suggesting a specific effect of intrauterine programming rather than child obesity per se. While alterations in the hypothalamic response were not associated with child adiposity measures at the baseline visit, we observed that greater hypothalamic activity in response to glucose in children predicted greater increases in child BMI 1 year later, and the hypothalamic response to glucose partially mediated the association between exposure to maternal obesity and child's BMI increases. These findings are in line with animal models (8,9,12) and suggest that the altered hypothalamic responses to glucose during childhood are an early change that predicts and perhaps contributes to increased susceptibility to weight gain and obesity later in life.

Although genetic factors may contribute to the observed alterations in the hypothalamic response to glucose during childhood, our finding that the impact of GDM exposure was limited to cases diagnosed by 26 weeks' gestation provides evidence for a specific role of the intrauterine environment. In cases in which GDM was diagnosed prior to 26 weeks' gestation, PG levels were significantly higher after the 1-h 50-g glucose challenge compared with cases in which GDM was diagnosed >26 weeks' gestation, suggesting greater severity of hyperglycemia among the GDM cases diagnosed earlier in pregnancy, which may have played a role in fetal hypothalamic programming. In addition, our findings and prior work showing that exposure to GDM early in gestation was associated with greater risk for autism spectrum disorders in offspring suggest that the timing and/or severity of GDM exposure may have important neurodevelopmental effects with long-term health sequelae of offspring (27).

We did not observe significant associations between exposure to GDM and child BMI or body fat at 7–11 years of age or changes 1 year later. However, children exposed to GDM had greater waist-to-height ratios, a marker of abdominal adiposity, when compared with unexposed children. These findings are in line with prior reports showing that in utero exposure to GDM had a larger impact on abdominal adiposity than on overall adiposity during early childhood (35–37). Unlike GDM exposure, maternal prepregnancy BMI was significantly associated with all measures of adiposity in children. These results are consistent with prior studies in young children showing significant associations between exposure to maternal obesity, but not GDM, and childhood obesity in early childhood (3,38). Collectively, these findings suggest that maternal obesity may have a stronger or earlier impact than maternal GDM on the tendency to develop obesity during childhood.

Limitations

The PASL methods used in this study provide a measure of changes in CBF, an indirect marker of neuronal activity. PASL at its current resolution cannot distinguish activity within the hypothalamus. Thus, our study could not distinguish between activation of hypothalamic areas involved in hunger and areas involved in satiety. We could not obtain maternal insulin concentrations during pregnancy and thus could not examine how maternal insulin resistance during pregnancy affected child outcomes. Our study design does not allow a causal inference to be made regarding the role of altered brain pathways on the development of obesity in children. Childhood obesity is a multifactorial disease process, and exposures to maternal GDM and obesity in utero may be two of many factors that contribute to increased obesity risk.

Conclusion

Intrauterine exposure to maternal obesity and separately to maternal GDM diagnosed relatively early in pregnancy alter glucose-induced hypothalamic activity in children. The altered hypothalamic response to glucose in children predicts greater increases in BMI 1 year later and partly explains the association between maternal obesity and increases in child's BMI 1 year later. Increased glucose-linked hypothalamic activation during childhood represents a possible mechanism by which in utero exposure to maternal metabolic disorders increases the risk for obesity later in life.

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