Received: 9 February 2023 | Revised: 22 March 2023 | Accepted: 4 April 2023

DOI: 10.1002/oby.23901

OBESITY SYMPOSIUM

Pediatric Obesity

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Associations among prenatal exposure to gestational diabetes mellitus, brain structure, and child adiposity markers

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Funding information
National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Numbers: K01DK115638, R03DK129186; National Institute of Mental Health, Grant/Award Number: F32MH12205

Abstract

Objective: The aim of this study was to investigate the mediating role of child brain structure in the relationship between prenatal gestational diabetes mellitus (GDM) exposure and child adiposity.

Methods: This was a cross-sectional study of 9– to 10-year-old participants and siblings across the US. Data were obtained from the baseline assessment of the Adolescent Brain Cognitive Development (ABCD) Study®. Brain structure was evaluated by magnetic resonance imaging. GDM exposure was self-reported, and discordance for GDM exposure within biological siblings was identified. Mixed effects and mediation models were used to examine associations among prenatal GDM exposure, brain structure, and adiposity markers with sociodemographic covariates.

Results: The sample included 8521 children (7% GDM-exposed), among whom there were 28 sibling pairs discordant for GDM exposure. Across the entire study sample, prenatal exposure to GDM was associated with lower global and regional cortical gray matter volume (GMV) in the bilateral rostral middle frontal gyrus and superior temporal gyrus. GDM-exposed siblings also demonstrated lower global cortical GMV than unexposed siblings. Global cortical GMV partially mediated the associations between prenatal GDM exposure and child adiposity markers.

Conclusions: The results identify brain markers of prenatal GDM exposure and suggest that low cortical GMV may explain increased obesity risk for offspring prenatally exposed to GDM.

INTRODUCTION

Approximately one in five youth in the US, which translates into almost 15 million children and adolescents, are living with obesity [1], placing them at increased risk for diabetes and cardiovascular disease [2]. Reducing the incidence of childhood obesity would have a consequential impact on the individual and socioeconomic burdens associated with obesity; however, existing strategies for treating adult obesity do not achieve long-lasting weight loss in this younger population [3, 4], and more than 90% of youth with obesity will continue to be classified as having overweight or obesity in adulthood [5, 6]. Improved understanding of risk factors for pediatric obesity will advance our knowledge of how obesity develops and guide interventions to mitigate short- and long-term disease risks.

Offspring exposed to gestational diabetes mellitus (GDM) prenatally have an increased risk of developing pediatric obesity [7–10], including higher body mass index (BMI), waist-to-hip circumference, and waist to height ratio (WHtR) [11–13]. Furthermore, the BMI of offspring exposed to GDM is greater than that of their siblings who were not exposed to GDM [14, 15], suggesting that the effect of prenatal GDM exposure on offspring BMI is independent of shared genetics and environment. The high prevalence and persistence of childhood obesity highlight the importance of understanding the underlying mechanisms.

Although the mechanisms for increased obesity risk in GDM-exposed offspring are unknown, existing studies suggest a neural basis. Serum levels of neurotrophins, including nerve growth factor and brain-derived neurotrophic factor—essential for neuronal growth, development, and differentiation—are lower in pregnant women with diabetes [16] and infants prenatally exposed to GDM [17]. Offspring exposed to GDM prenatally demonstrate brain structural alterations, such as presence of hypothalamic gliosis [18, 19], lower white matter integrity in sensorimotor regions [20], lower cortical excitability [21], and mixed results on hippocampal thickness [22, 23]. However, prior work is hampered by small sample sizes and poor representation of diverse populations. Prior studies are also limited in their ability to establish mediating relationships among prenatal exposure to GDM, brain structure, and adiposity in children. Moreover, it remains to be determined whether neural correlates of prenatal GDM exposure are independent of shared genetics and environment.

To elucidate gaps in the literature, we leveraged brain and anthropometric data in children aged 9 to 10 years old from the Adolescent Brain Cognitive Development (ABCD) Study®—the largest and most diverse pediatric neuroimaging study to date [24]. We examined relationships between prenatal exposure to GDM and brain structural measures (i.e., cortical and subcortical volumes, cortical thickness, and surface area). Furthermore, a mediation analysis was performed to investigate whether brain structural measurements mediated associations between prenatal GDM exposure and adiposity markers in children. The ABCD study also includes siblings discordant for GDM exposure, providing the opportunity to control for shared genetics and environment. We hypothesized that GDM-exposed children (vs. unexposed children) would have smaller brain structural measures (e.g., volumes, cortical thickness, surface area), independently of shared genetics and environment; brain structural measures would partially mediate associations of GDM exposure with adiposity markers in children. To our knowledge, this is one of the largest and most highly powered neuroimaging studies to identify robust brain signatures of prenatal exposure to GDM, thereby enhancing our understanding of etiologic pathways of obesity development.

Study Importance

What is already known?

- Children exposed to gestational diabetes mellitus (GDM) prenatally have higher adiposity measures (BMI, waist-to-hip circumference, waist to height ratio) and increased risk of developing obesity.

What does this study add?

- We provide evidence that prenatal exposure to GDM and smaller cortical gray matter volume (GMV) are associated, independently of shared genetics and environment, in a large and diverse cohort of 8521 children.
- Cortical GMV partially mediated the associations of prenatal GDM exposure and adiposity markers in children, which may contribute to increased obesity risk in offspring exposed to GDM.

How might these results change the direction of research or the focus of clinical practice?

- It is important for clinicians to be aware of detrimental effects of diabetes during pregnancy on the developing brain in offspring.
- Future study should examine potential interventions that may mitigate adverse effects of prenatal GDM exposure on offspring brain development, thereby reducing obesity risk.

METHODS

Participants

ABCD is a 10-year, large-scale, longitudinal study of pediatric brain and cognitive development in the US. Participants and siblings were initially recruited from a randomized sample of schools within range of 21 sites across four major regions of the US (Northeast, Midwest, South, and West). Recruitment was optimized to accurately represent the sociodemographic diversity of the US, and Institutional Review Board (IRB) approval was obtained from the centralized IRB at the University of California, San Diego (IRB# 160091), as well as at each data collection site.

Data for this project were obtained from the ABCD 3.0 data release (DOI:10.15154/1524739), and they focused on baseline assessments collected from September 1, 2016, to October 15, 2018. Participants were excluded if they met the following criteria: not fluent in English, history of seizures, birth more than 12 weeks premature, birth weight less than 1200 g, complications at birth, substance use disorder, intellectual disability, traumatic brain injury, brain tumor, stroke, aneurysm, brain hemorrhage, subdural hematoma, cerebral palsy, diabetes, lead poisoning, muscular dystrophy, autism spectrum disorder, and other medical conditions considered exclusionary. Additional exclusion criteria were applied based on anthropometric measurements, neuroimaging, and other covariates as described in the following sections, resulting in a final sample of 8521 participants (Supporting Information Figure S1). Briefly, participants were included only if their anthropometric and neuroimaging measurements passed quality control and if they had complete data for additional covariates.

GDM exposure

GDM exposure was self-reported by the parent during baseline assessment via a question: "During the pregnancy with this child, did you/biological mother have pregnancy-related diabetes?" and coded as a binary variable.

Biological siblings with discordance for GDM exposure were restricted to participants who shared the same mother. Birth order was calculated based on interview age and interview date.

Anthropometric measures

Children's weight, height, and waist circumference were measured at baseline by a trained researcher. Waist circumference was measured with a tape around the highest point on the pelvic bone. Height (in inches) and weight (in pounds) were recorded as the mean of up to three separate measurements. These measures were used to calculate WHtR and BMI (kg/m^2).

Age- and sex- specific BMI percentiles, BMI *z* scores, weight *z* scores, and height *z* scores were calculated according to the Centers for Disease Control and Prevention (CDC) guidelines [25]. Childhood weight status was defined using CDC guidelines: obesity (≥95th percentile), overweight (≥85th percentile to <95th percentile), normal weight (≥5th percentile to <85th percentile), and underweight (<5th percentile). Waist *z* scores were calculated based on National Health and Nutrition Examination Survey (NHANES) III data. The following criteria were used to exclude implausible anthropometric data following procedures used in previous studies [26–29]: (1) BMI *z* scores ≤ −4 standard deviations (SDs) or ≥8 SDs, (2) BMI <10, (3) weight *z* scores ≤ −5 SDs or ≥8 SDs, (4) height *z* scores < −5 SDs or >4 SDs, (5) waist *z* scores < −4 SDs or >4 SDs, and (6) WHtR ≤0.3 or ≥1.

Neuroimaging

Magnetic resonance imaging (MRI) data collection methods were optimized for 28 3-T scanners across 21 ABCD study sites [30]. FreeSurfer (version 5.3.0, https://surfer.nmr.mgh.harvard.edu/) was used for cortical surface reconstruction and subcortical segmentation, based on the T1-weighted anatomical scans, producing the following measures: cortical and subcortical gray and white matter volumes (mm^3), regional cortical thickness (mm), and regional cortical surface area (mm^2) using the Desikan–Killiany Atlas.

Neuroimaging analyses excluded participants who had abnormal radiological findings or whose T1 scan was of insufficient quality, as determined by the ABCD Data Analytics and Informatics Center [30]. Participants were also excluded based on quality control procedures on the cortical surface reconstruction for five categories of inaccuracy: severity of motion, intensity inhomogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact [30].

Covariates

Sex was based on caregiver's report of child's sex at birth. Age was the child's age in months at baseline interview. Race/ethnicity was categorized into five groups: Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and other. Parental education was modeled as a binary variable indicating whether at least one parent had obtained a bachelor's degree. Yearly household income was quantified as an ordinal range, which included three categories: <$50,000, ≥$50,000 and <$100,000, and ≥$100,000. Pubertal stage was calculated using the parent-report pubertal development scale and reduced to three levels, prepubertal, early pubertal, and mid- to postpubertal stage.

Data analysis

Primary analysis

Linear mixed-effects models were used to examine associations of GDM exposure (independent variable) with global brain measurements and adiposity markers (dependent variables). Global brain measurements included total cortical surface area, mean cortical

thickness, total cortical gray matter volume (GMV), subcortical GMV, and cerebral white matter volume. Adiposity measures included BMI *z* score, waist circumference, and WHtR.

Two sets of models were fit. The first set of models included the full sample. Family ID, nested within the site, was modeled as a random intercept to account for shared variation related to study visit location and family membership. Covariates included sociodemographic variables such as age, sex assigned at birth, pubertal status, race/ethnicity, family income, and parental education. Age and sex were not included as covariates for models with BMI *z* score as a dependent variable. Imaging analyses also included scanner model, handedness, and intracranial volume (ICV) for volumetric measures. Additional models were fitted to adjust for (1) gestational age at birth, (2) other maternal health problems during pregnancy, (3) child health problems at birth, and (4) maternal alcohol or tobacco use during pregnancy (Supporting Information Methods). To follow up with significant associations of GDM exposure with global brain measures, we conducted region of interest (ROI) analysis.

Subanalysis

A second set of model fits was performed only in sibling pairs discordant for GDM exposure. Models included family ID as a random intercept and they were adjusted for birth order, sex, pubertal status, race/ethnicity, family income, parental education, handedness, and ICV for volumetric analyses. Site and scanner were excluded due to insufficient sample size. Age was not adjusted for as it was highly correlated with birth order in this sample.

Mediation analysis

Mediation analysis was completed with the hypothesis that the correlation between prenatal GDM exposure and adiposity markers was mediated by brain structural measurements, using the *mediation* package in R. First, confounding covariates (i.e., sociodemographic variables, scanner, handedness, and ICV) were regressed out of adiposity and brain structural variables using regressions. Next, separate components of the possible mediation paths were assessed (A: correlation between GDM exposure and brain; B: correlation between GDM exposure and adiposity; C: correlation between brain and adiposity in a model that also includes GDM exposure). Mediation was then tested in models where all component paths were significant. Nonparametric bootstrapped percentile confidence intervals (CI) were estimated from 1000 simulations.

Analyses used linear mixed effects models in R with the *lme4* package. Standardized betas were reported. The 95% Wald CI were calculated based on the local curvature of the likelihood surface. Cohen *d* effect sizes were calculated from least-squares means, model residual SDs, and residual degrees of freedom using the *emmeans* package. *P* values were calculated using Satterthwaite's method in the *lmerTest* package. Tests of significance (two-tailed) were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR), with $p < 0.05$ as the corrected threshold for significance.

RESULTS

Participant demographics

Characteristics of the sample are described in Table 1. Around 7% of children were prenatally exposed to GDM and they differed from unexposed children in terms of race/ethnicity ($\chi^2(4) = 29.505$, $p < 0.001$), family income ($\chi^2(2) = 11.728$, $p = 0.003$), parental education ($\chi^2(1) = 16.988$, $p < 0.001$), and pubertal status ($\chi^2(2) = 10.960$, $p = 0.028$).

Among sibling pairs discordant for GDM exposure, higher rates of GDM exposure were found in the older siblings than younger ones (71% vs. 29%, $\chi^2(1) = 8.643$, $p = 0.003$). Siblings discordant for GDM exposure (Supporting Information Table S1) did not differ in sex ($\chi^2(1) = 0.072$, $p = 0.789$), pubertal status ($\chi^2(2) = 0.763$, $p = 0.683$), race/ethnicity ($\chi^2(4) = 0.821$, $p = 0.936$), family income ($\chi^2(2) = 0$, $p = 1$), and parental education ($\chi^2(1) = 0$, $p = 1$).

GDM exposure and child global and regional brain measurements

Prenatal exposure to GDM was associated with smaller total cortical GMV after FDR correction (β [95% CI] = −0.051 [−0.089, −0.013], FDR-corrected $p = 0.045$, Figure 1A, Table 2). Effect sizes (Cohen *d*) for GDM-exposed versus unexposed children in global brain measures ranged from −0.089 to −0.160. Total cortical surface area and subcortical GMV trended toward significance after FDR correction. Unadjusted results are included in Supporting Information Table S2. In a subset of the sample with sibling pairs discordant for GDM exposure, total cortical GMV was also lower in GDM-exposed siblings than unexposed siblings (β [95% CI] = −0.284 [−0.531, −0.037], $p = 0.034$, Figure 1A).

ROI analysis (Table 2, Figure 1B) found that prenatal exposure to GDM was associated with smaller cortical GMV in the bilateral rostral middle frontal gyrus (MFG) (β [95% CI]= −0.087 [−0.143, −0.031], $p = 0.042$) and superior temporal gyrus (STG) (β [95% CI]= −0.098 [−0.154, −0.043], $p = 0.017$). The effect size for GDM-exposed versus unexposed children in the MFG and STG was −0.179 and −0.195, respectively. Results for global and regional cortical GMV remained largely the same after additional adjustment for gestational age, other maternal health problems during pregnancy, child health problems at birth, or maternal alcohol/tobacco use during pregnancy (Supporting Information Results, Supporting Information Table S3–S10).

Given prior studies reported conflicting results for the association of prenatal GDM exposure and hippocampal GMV, for completeness, we present ROI analysis results for subcortical regions Supporting Information Table S11. There were no significant associations between prenatal GDM exposure and GMV in any subcortical ROIs.

TABLE 1 Sample characteristics by gestational diabetes mellitus status

	Exposed ($N = 578$)	Unexposed ($N = 7943$)	All ($N = 8521$)	p value[a]
Age (y), mean ± SD	9.92 ± 0.62	9.92 ± 0.63	9.92 ± 0.63	0. 802
Sex				0.587
Female	274 (47.4%)	3864 (48.6%)	4138 (48.6%)	
Male	304 (52.6%)	4079 (51.4%)	4383 (51.4%)	
Race/ethnicity				**<0.001**
White	277 (47.9%)	4510 (56.8%)	4787 (56.2%)	
Black	72 (12.5%)	991 (12.5%)	1063 (12.5%)	
Hispanic	127 (22.0%)	1521 (19.1%)	1648 (19.3%)	
Asian	19 (3.3%)	121 (1.5%)	140 (1.6%)	
Other	83 (14.4%)	800 (10.1%)	883 (10.4%)	
Family income				**0.003**
<$50,000	189 (32.7%)	2207 (27.8%)	2396 (28.1%)	
≥$50,000 and <$100,000	177 (30.6%)	2261 (28.5%)	2438 (28.6%)	
≥$100,000	212 (36.7%)	3475 (43.7%)	3687 (43.3%)	
Parental education (highest)				**<0.001**
No bachelor's degree	260 (45.0%)	2885 (36.3%)	3145 (36.9%)	
Bachelor's degree or higher	318 (55.0%)	5058 (63.7%)	5376 (63.1%)	
Pubertal stage				**0.028**
Prepuberty	272 (47.1%)	4173 (52.5%)	4445 (52.2%)	
Early puberty	141 (24.4%)	1857 (23.4%)	1998 (23.4%)	
Mid–post puberty	165 (28.5%)	1913 (22.6%)	2078 (24.4%)	
Weight categorization				**<0.001**
Underweight	16 (2.8%)	308 (3.9%)	324 (3.8%)	
Normal weight	319 (55.2%)	5287 (66.6%)	5606 (65.8%)	
Overweight	105 (18.2%)	1137 (14.3%)	1242 (14.6%)	
Obesity	138 (23.9%)	1211 (15.2%)	1349 (15.8%)	

Note: Bold indicates statistical significance ($p < 0.05$).
[a]Categorical variables by χ^2 test and continuous variables by t test.

GDM exposure and child adiposity markers

GDM exposure was associated with a higher likelihood of being classified as having overweight or obesity (42% vs. 29%: $X^2(3) = 43.160$, $p < 0.001$). Children exposed to GDM (vs. unexposed children) had higher adiposity markers (BMI z score: β [95% CI] = 0.175 [0.093, 0.256], FDR-corrected $p < 0.001$; waist circumference: β [95% CI] = 0.201 [0.121, 0.281], FDR-corrected $p < 0.001$; WHtR: β [95% CI] = 0.199 [0.119, 0.280], FDR-corrected $p < 0.001$) (Supporting Information Figure S2).

Mediation relationships among GDM exposure, brain structure, and adiposity markers

Global cortical GMV partially mediated the relationship between GDM exposure and BMI z score, with a significant indirect effect (mediated effect [95% CI] = 0.007 [0.002, 0.096], $p = 0.012$). The direct effect of GDM on BMI z score was reduced from β [95% CI] = 0.168 [0.077, 0.255], $p < 0.001$ to β [95% CI] = 0.161 [0.072, 0.247], $p < 0.001$ in the presence of the mediator (Figure 2), indicating a partial mediation. Global cortical GMV also partially mediated the relationships between GDM exposure and waist circumference (mediated effect [95% CI] = 0.008 [0.002, 0.015], $p = 0.012$) and WHtR (mediated effect [95% CI] = 0.005 [0.001, 0.009], $p = 0.012$) (Supporting Information Table S12).

DISCUSSION

This is the first large, multisite study investigating relationships among prenatal exposure to GDM, brain structure, and adiposity markers in a diverse cohort of 8521 children. We found that prenatal exposure to GDM was associated with lower global cortical GMV in the entire study sample, as well as a subset of the sample including siblings discordant for GDM exposure, and global cortical GMV, in part, mediated relationships between prenatal GDM exposure and adiposity markers in children. The results identified robust brain

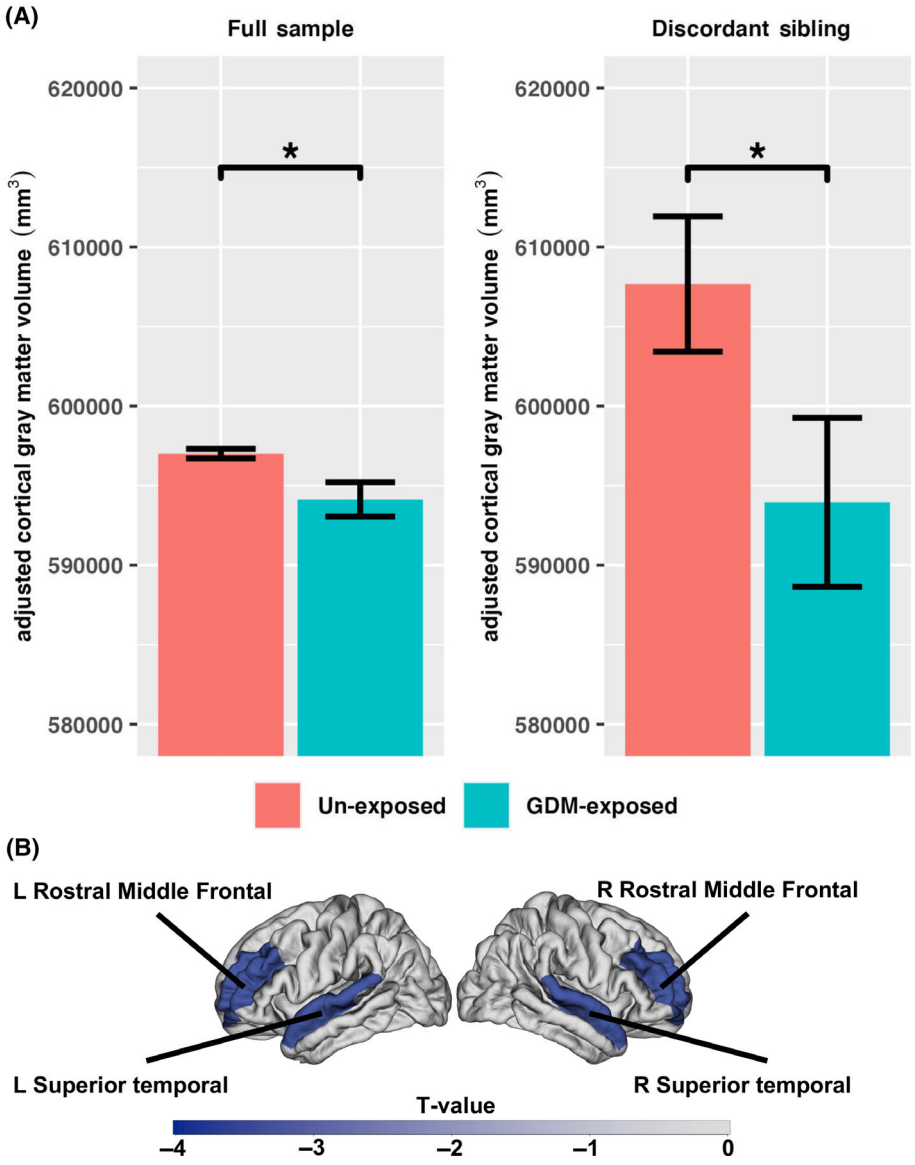

FIGURE 1 Relationships between exposure to gestational diabetes mellitus (GDM) and child brain structure. (A) Bar plots display mean ± 95% CI of adjusted cortical gray matter volume, separated by prenatal GDM exposure status. Statistics for full sample adjusted for family ID nested within site, scanner model, handedness, age, sex, pubertal status, race/ethnicity, family income, and parental education, and statistics for subsample of siblings discordant for GDM exposure adjusted for family ID, handedness, birth order, sex, pubertal status, race/ethnicity, family income, and parental education. * indicates statistical significance ($p < 0.05$). (B) Association between GDM exposure and child regional cortical gray matter volume in the significant regions of interest. The *t* score denotes regions significantly associated with GDM exposure from linear mixed effects models (FDR-corrected $p < 0.05$) where family ID nested within site, as well as subject, was included as random effects, and age, sex, pubertal status, race/ethnicity, family income, parental education, scanner model, intracranial volume, and handedness were included as fixed effects. Region of interest analysis was bilateral in the models. [Color figure can be viewed at wileyonlinelibrary.com]

signatures of prenatal GDM exposure and suggested that low cortical GMV may contribute to increased obesity risk in offspring exposed to GDM.

A link between prenatal GDM exposure and altered neural structure has been previously described [13, 18, 20, 22, 31]; however, interpretation has been constrained by methodological limitations, including small sample sizes, poor representation of diverse populations, and lack of controlling for shared genetics and environment. Capitalizing on the large and diverse sample of the ABCD study, we were able to identify neural signatures of prenatal GDM exposure, including lower global cortical GMV and regional cortical GMV in the bilateral MFG and STG, with small to moderate effect sizes in youth aged between 9 and 10 years. Incorporating covariates known to influence brain development, including gestational age, other maternal health problems during pregnancy (e.g., high blood pressure, preeclampsia), child health problems at birth, and maternal alcohol/tobacco use during pregnancy, did not impact the results. The effect sizes observed here were significant yet small. This was expected because MRI scans were conducted 9 to 10 years after prenatal GDM exposure, and development across the first decade of life is influenced

TABLE 2 Associations between gestational diabetes mellitus exposure and global and regional brain measurements

Model	β[a]	95% CI[b]	*p* value	FDR-adjusted *p* value[c]	Cohen *d*
Global brain measurements					
Total cortical surface area (mm^2)	−0.073	(−0.144, −0.003)	0.042	0.069	−0.144
Mean cortical thickness (mm)	−0.057	(−0.132, 0.017)	0.132	0.132	−0.089
Cortical gray matter volume (mm^3)	−0.051	(−0.089, −0.013)	0.009	**0.045**	−0.160
Subcortical gray matter volume (mm^3)	−0.048	(−0.095, −0.001)	0.044	0.074	−0.128
Cerebral white matter volume (mm^3)	−0.024	(−0.062, 0.014)	0.220	0.220	−0.079
Regional cortical gray matter volume (mm^3)					
Banks of the superior temporal sulcus	−0.037	(−0.097, 0.022)	0.217	0.393	−0.048
Caudal anterior cingulate cortex	0.003	(−0.055, 0.060)	0.924	0.924	0.003
Caudal middle frontal gyrus	−0.016	(−0.077, 0.045)	0.607	0.765	−0.026
Cuneus cortex	−0.083	(−0.145, −0.021)	0.009	0.097	−0.130
Entorhinal cortex	0.059	(−0.004, 0.122)	0.066	0.250	0.078
Fusiform gyrus	−0.029	(−0.086, 0.027)	0.305	0.494	−0.050
Inferior parietal cortex	−0.032	(−0.089, 0.026)	0.284	0.482	−0.057
Inferior temporal gyrus	0.036	(−0.020, 0.093)	0.209	0.393	0.064
Isthmus cingulate cortex	−0.012	(−0.071, 0.047)	0.681	0.772	−0.019
Lateral occipital cortex	−0.052	(−0.107, −0.004)	0.067	0.250	−0.098
Lateral orbital frontal cortex	−0.044	(−0.099, −0.011)	0.116	0.328	−0.092
Lingual gyrus	−0.058	(−0.124, 0.007)	0.082	0.253	−0.115
Medial orbital frontal cortex	−0.012	(−0.068, 0.044)	0.678	0.772	−0.018
Middle temporal gyrus	−0.040	(−0.094, −0.014)	0.146	0.354	−0.079
Parahippocampal gyrus	0.025	(−0.038, 0.087)	0.440	0.676	0.034
Paracentral lobule	−0.040	(−0.102, 0.022)	0.211	0.393	−0.055
Pars opercularis	−0.018	(−0.080, 0.044)	0.566	0.740	−0.025
Pars orbitalis	−0.055	(−0.116, 0.005)	0.074	0.250	−0.079
Pars triangularis	−0.020	(−0.086, 0.047)	0.047	0.560	−0.028
Pericalcarine cortex	−0.089	(−0.159, −0.020)	0.118	0.100	−0.181
Postcentral gyrus	−0.037	(−0.096, 0.022)	0.220	0.393	−0.066
Posterior cingulate cortex	0.008	(−0.066, 0.110)	0.620	0.787	0.011
Precentral gyrus	0.020	(−0.035, 0.075)	0.477	0.677	0.038
Precuneus cortex	−0.035	(−0.090, 0.020)	0.216	0.393	−0.078
Rostral anterior cingulate cortex	−0.013	(−0.070, 0.044)	0.654	0.772	−0.017
Rostral middle frontal gyrus	−0.087	(−0.143, −0.031)	0.002	**0.042**	−0.179
Superior frontal gyrus	−0.054	(−0.106, −0.002)	0.042	0.0236	−0.120
Superior parietal cortex	−0.044	(−0.104, 0.015)	0.146	0.354	−0.086
Superior temporal gyrus	−0.098	(−0.154, −0.043)	<0.001	**0.017**	−0.195
Supramarginal gyrus	−0.009	(−0.065, 0.047)	0.748	0.820	−0.013
Frontal pole	−0.006	(−0.069, 0.057)	0.848	0.873	−0.008
Temporal pole	0.024	(−0.042, 0.090)	0.472	0.676	0.031
Transverse temporal cortex	−0.077	(−0.141, −0.013)	0.019	0.130	−0.113
Insular cortex	−0.051	(−0.106, 0.004)	0.069	0.250	−0.125

[a]A positive β corresponds to larger measurements in the GDM-exposed group, whereas a negative β corresponds to the opposite.
[b]Regression coefficients (95% CI) from linear mixed-effects models. For regional cortical measurements, coefficients (95% CI) represent main effect estimate of prenatal exposure to GDM. GDM exposure by hemisphere interactions was modeled but not significant in any region of interest.
[c]Multiple comparisons were conducted with Benjamini–Hochberg FDR correction. Boldface indicates significance at the corrected threshold of $p < 0.05$.

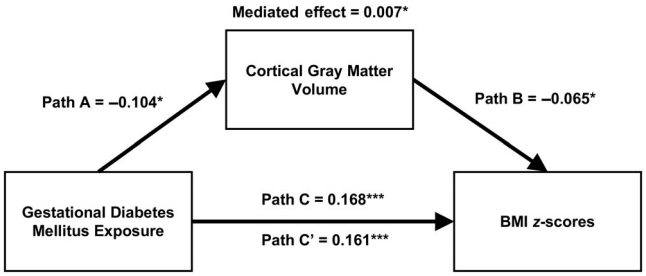

FIGURE 2 Cortical gray matter volume partially mediating the relationship between gestational diabetes mellitus (GDM) exposure and BMI *z* score. Variation based on pubertal status, race/ethnicity, family income, and parental education was regressed out of BMI *z* score, and additional variation based on scanner, intracranial volume, and handedness was regressed out of cortical gray matter volume prior to conducting mediation modeling. Reported values for Paths A, B, C, and C′ indicate standardized regression coefficients for each path. Paths B and C' indicate standardized multiple regression coefficients of GDM exposure (C′) and cortical GMV (B) in predicting BMI *z* score. The mediated effect indicates the reduced direct effect of GDM exposure on BMI *z* score when the mediator is included in this model. $^{*}p < 0.05$, $^{***}p < 0.001$

by many other factors. It is worth noting that our effect sizes are comparable with other changes observed in the context of brain disorders including attention-deficit/hyperactivity disorder, autism spectrum disorder, obsessive-compulsive disorder, and major depressive disorder [32–34]. Data from sibling pairs discordant for GDM exposure also demonstrated lower total cortical GMV in GDM-exposed siblings than unexposed siblings, suggesting that GDM exposure itself likely contributes to low cortical GMV because sibling design allows for controlling for shared genetics and family environment.

Our analysis identified a selective impact of prenatal GDM exposure on the MFG and STG. The frontal and temporal regions follow a protracted developmental trajectory, an inverted U-shape trajectory with a preadolescent increase followed by a postadolescent decrease [35], which render them particularly vulnerable to early insult, such as that inflicted by GDM exposure. A recent study using the ABCD data set reported that lower GMV in the MFG is associated with greater concurrent BMI *z* score and greater changes in BMI *z* score in 1 year [36]. Together, these results suggest that GDM-induced changes in cortical GMV may be associated with both current and future weight status. Although the functional significance of GDM exposure–associated alterations in cortical GMV remains to be established, we can reasonably speculate that functional deficits in cortical areas implicated in dietary self-regulation may lead to greater adiposity in children exposed to GDM given that (1) cortical regions, particularly the MFG, play a critical role in self-regulation, including top-down regulation of craving and food consumption [37, 38], and (2) smaller cortical GMV in prefrontal areas was shown to be associated with poorer self-regulation [39], which is tightly linked to overeating and obesity [40]. Additional studies using the ABCD data set have found other neural correlates of obesity or weight gain, including lower cortical thickness (primarily in the prefrontal cortex) [27] and higher cell density in the nucleus accumbens [41]. We recognize that GDM exposure is one of many factors contributing to childhood obesity; thus, other obesity-associated risk factors may be contributing to the changes in neural structure. In contrast to animal studies [42–44] and a recent human study [22], we and others [23] did not identify a significant association of GDM exposure with hippocampal GMV in children. We speculate that this inconsistency may be due to assessment of specific subregions of the hippocampus by former studies versus whole hippocampus by latter studies.

Although alterations in brain development are hypothesized as a potential mechanism for obesity risk in GDM-exposed offspring, this hypothesis has not been fully tested in humans. In this study, we tested whether alterations in global cortical GMV contribute to higher adiposity measures in GDM-exposed children using mediation models. We found that global cortical GMV partially mediated the associations between prenatal exposure to GDM and adiposity markers in children. These findings expand on prior studies [13, 31] by showing direct evidence of the mediating role of the brain in the associations of prenatal exposure to GDM and offspring adiposity and provide a neurobiological explanation of increased obesity risk in GDM-exposed offspring. Given the cross-sectional nature of ABCD baseline data, causality cannot be established. Additionally, we cannot exclude other possible mediating relationships between prenatal GDM exposure, brain structure, and adiposity in children.

Our findings have important clinical implications. This was a well-powered study with more than 8500 children from different demographic and socioeconomic backgrounds, demonstrating that there were adverse effects of prenatal exposure to GDM on brain development in children. It is important for clinicians to be aware of detrimental effects of diabetes during pregnancy on the developing brain in offspring. Future studies should examine potential interventions that may mitigate adverse effects of prenatal GDM exposure on offspring brain development, thereby reducing obesity risk.

Our study also includes some limitations. GDM exposure was self-reported; however, the reported prevalence in the ABCD study was comparable with the estimated rate of GDM in the US. Detailed information on treatment and severity of diabetes in pregnancy was not available; thus, we were not able to assess relationships between those variables and child brain structure. The ABCD study did not record maternal obesity status during pregnancy, which is closely related to maternal diabetes. Our prior work showed overlapping and differential effects of maternal obesity exposure and GDM exposure on children's brain metabolic and reward circuitry [13, 31, 45]. Thus, we speculate that maternal obesity exposure may have similar or separate effects from those of maternal diabetes in global and regional cortical GMV. Covariates included in the models were limited to those available in the ABCD study. Another limitation included use of the default brain atlas for imaging analysis. The ABCD study largely represented the diversity of US populations. In the current study, we used a subset of youth enrolled in the ABCD cohort, but exclusion criteria did not change the sample distribution negatively. However, our results did not incorporate survey weights and thus may have limited generalizability.

CONCLUSION

In conclusion, prenatal GDM exposure and smaller cortical GMV are associated independently of genetics and shared environment, and in turn, GMV is related to greater markers of adiposity in children. Low cortical GMV may be a potential neural mechanism by which prenatal GDM exposure mediates obesity risk in offspring.O

AUTHOR CONTRIBUTIONS

Shan Luo and Eustace Hsu performed the statistical analysis and drafted the manuscript. All authors provided review, commentary, and revisions to the manuscript and approved the final manuscript as submitted. Shan Luo is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the National Institute of Mental Health (NIMH) Data Archive (NDA). This is a multisite longitudinal study designed to recruit more than 10,000 children aged 9 to 10 years and follow them over 10 years into early adulthood. The ABCD study is supported by the NIH and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, and U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD study consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD study consortium investigators. The ABCD study data repository grows and changes over time.

FUNDING INFORMATION

This work was supported by the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases K01DK115638 (PI: SL), R03DK129186 (PI: SL) and USC Diabetes and Obesity Research Institute Pilot Award (PI: SL). This study was partially supported by National Institute of Mental Health (NIMH) F32MH12205 (PI: KL).

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Luo S, Hsu E, Lawrence KE, et al. Associations among prenatal exposure to gestational diabetes mellitus, brain structure, and child adiposity markers. *Obesity (Silver Spring)*. 2023;31(11):2699-2708. doi:10.1002/oby.23901