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Mother-child cardiometabolic health 4–10 years after pregnancy complicated by obesity with and without gestational diabetes

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Abstract

Objective: Obesity in pregnancy and gestational diabetes (GDM) increase cardiometabolic disease risk but are difficult to disentangle. This study aimed to test the hypothesis that 4–10 years after a pregnancy complicated by overweight/obesity and GDM (OB-GDM), women and children would have greater adiposity and poorer cardiometabolic health than those with overweight/obesity (OB) or normal weight (NW) and no GDM during the index pregnancy.

Methods: In this cross-sectional study, mother-child dyads were stratified into three groups based on maternal health status during pregnancy (OB-GDM = 67; OB = 76; NW = 76). Weight, height, waist and hip circumferences, and blood pressure were measured, along with fasting glucose, insulin, HbA1c, lipids, adipokines, and cytokines.

Results: Women in the OB and OB-GDM groups had greater current adiposity and poorer cardiometabolic health outcomes than those in the NW group ($p < 0.05$). After adjusting for current adiposity, women in the OB-GDM group had higher HbA1c, glucose, HOMA-IR and triglycerides than NW and OB groups ($p < 0.05$).

Among children, adiposity was greater in the OB-GDM versus NW group ($p < 0.05$), but other indices of cardiometabolic health did not differ.

Conclusions: Poor cardiometabolic health in women with prior GDM is independent of current adiposity. Although greater adiposity among children exposed to GDM is evident at 4–10 years, differences in cardiometabolic health may not emerge until later.

KEYWORDS
adiposity, diabetes, intrauterine programming, metabolic health, pregnancy

1 | INTRODUCTION

Women with overweight or obesity have greater risk for adverse outcomes during pregnancy including gestational diabetes mellitus (GDM),[1] and it is estimated that almost half of all cases of GDM are attributable to pre-pregnancy overweight or obesity.[2] Beyond pregnancy, women with overweight or obesity in pregnancy, with or without GDM, have greater risk for developing cardiometabolic disease in the future, including metabolic syndrome, cardiovascular disease, type 2 diabetes, and specific cancers.[3-8] Consequently, even though obesity-related complications such as GDM resolve postpartum, their presentation during pregnancy serves as a signal that women are susceptible to future cardiometabolic disease. Given that so many women with GDM have overweight or obesity during and after pregnancy, it is difficult to disentangle the association of maternal overweight or obesity, versus GDM, on women's future health. Direct comparison between women with a history of overweight/obesity in pregnancy *with* GDM, to those with overweight/obesity in pregnancy *without* GDM, is needed to understand the relative contribution of each condition to future cardiometabolic health.

In addition to long term risks for women, children exposed to maternal overweight/obesity or GDM in utero are also at risk for obesity and cardiometabolic disease. *In utero* exposure to maternal obesity, even in the absence of GDM, is associated with greater body weight and total adiposity, central or abdominal obesity, hyperinsulinemia, high blood pressure, and lower HDL-cholesterol concentrations.[9-11] Children exposed to GDM in utero also exhibit greater total and central obesity, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, and high blood pressure.[12-15] The degree to which adverse cardiometabolic outcomes in offspring are associated with maternal overweight/obesity distinct from GDM is not clear.

Few prior studies have concurrently investigated maternal and child body composition and cardiometabolic outcomes in the years following pregnancy. This approach could yield valuable information about the degree to which children's cardiometabolic phenotype is similar to that of mothers, and whether mother-child associations differ for dyads with low risk for obesity and disease versus those with greater risk for obesity and disease. A study of mothers and 15 year-old daughters showed that mothers with prior GDM were more likely to have developed impaired glucose tolerance than those who were glucose tolerant in pregnancy, and their daughters had more central adiposity and insulin resistance.[16] The Hyperglycemia and Adverse Pregnancy Outcomes Follow-up Study reported that 10–14 years after the index pregnancy, women with prior GDM were more likely to have developed prediabetes or type 2 diabetes, and their children had greater adiposity and waist circumference, lower insulin sensitivity, and greater risk for impaired glucose tolerance, as compared to those born to women without GDM.[13,17] These findings imply that when a pregnancy is complicated by GDM, women and children share a common risk for glucose metabolism disorders in the future. However, whether these maternal-child associations are evident prior to adolescence, and the degree to which shared risk is attributable to a history of GDM versus obesity, is less clear. Further, there is a dearth of research about whether other cardiometabolic biomarkers such as lipid profile, blood pressure, adipokines and cytokines are correlated in mothers and their children.

The goal of this study was to dissociate the effects of maternal overweight/obesity during pregnancy from those of GDM on mother-child body composition and cardiometabolic health 4–10 years after pregnancy. Mother-child dyads with an index pregnancy characterized by maternal overweight/obesity with GDM, maternal overweight/obesity without GDM, and maternal normal weight without GDM (referent group) were compared. Indices of cardiometabolic health included blood pressure, lipids (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides and free fatty acids [FFA]), markers of glucose metabolism (hemoglobin A1c [HbA1c], fasting glucose, fasting insulin, and the homeostatic model assessment of insulin resistance [HOMA-IR]). In addition, the adipokines leptin and adiponectin were measured because high leptin concentrations are associated with obesity, inflammation, and increased risk for cardiovascular disease[18] and low adiponectin concentrations are associated with insulin resistance and cardiovascular risk.[19] The cytokines c-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) were also compared across groups because these markers of inflammation are elevated with obesity, cardiovascular disease, glucose intolerance and type 2 diabetes.[20,21] It was hypothesized that dyads characterized by maternal overweight/obesity in pregnancy *and* GDM would have more total and central adiposity, and poorer cardiometabolic health, than those with

overweight/obesity or normal weight and no GDM during the index pregnancy. Given that women with overweight and obesity during the index pregnancy, and their children, were expected to have greater adiposity at the time of the study compared to those with normal weight in pregnancy, models were repeated with current adiposity as a covariate to investigate whether group differences were independent of (vs. attributable to), the current degree of adiposity. A secondary goal was to explore whether child body composition outcomes and indices of cardiometabolic health were correlated with those of mothers, in order to understand the degree to which children's phenotypes mimic those of mothers, and whether any such similarities are stronger among children with greater risk for future disease.

2 | METHODS

2.1 | Participants

Mother-child dyads were recruited into this cross-sectional study to fill three groups based on characteristics of an index pregnancy 4–10 years earlier: (1) maternal normal weight (BMI <25.0 kg/m^2) at the first prenatal care visit and no GDM (normal weight, NW); (2) maternal overweight or obesity (BMI ≥25.0 kg/m^2) at the first prenatal care visit and no GDM (overweight/obesity, OB); (3) maternal overweight or obesity (BMI ≥25.0 kg/m^2) at the first prenatal care visit and GDM (overweight/ obesity and GDM; OB-GDM). Participants were recruited from April 2017 to June 2019 by telephone follow up of potentially eligible women who received prenatal care at UAB during the years of interest, and through flyers and advertisements in social media and neighborhood applications. Women were eligible if aged 20–36 years at delivery, had a BMI at entry to prenatal care within the criteria for one of the three groups described above, and the child from the index pregnancy would be between 4.0 and 10.9 years of age on the date of enrollment in this study. Women with hepatitis B or C, lupus, heart disease, HIV, or renal disease during their index pregnancy were excluded from the study, as were those with opioid, other narcotic, or illicit drug use, or tobacco or alcohol use during the index pregnancy. GDM status during the index pregnancy was determined by review of prenatal records for women who received prenatal care at this institution (University of Alabama at Birmingham, UAB), and by self-report with later verification from medical records for those who delivered outside of this institution. From 2007 to 2015, the years during which women eligible for this study would have been pregnant, a two-step screening and diagnostic protocol was used to diagnose GDM at UAB. Women were screened with a non-fasting 50 g oral glucose challenge test, followed by the fasting 3 h oral glucose tolerance test (OGTT) for women with 1 h glucose of 135–199 mg/dl. GDM was diagnosed if women met the Carpenter and Coustan criteria based on their glucose concentrations during the OGTT.[22] If the 1 h screening glucose concentration was ≥200 mg/dl, a diagnosis of GDM could

be made and OGTT deferred. For non-UAB deliveries (21.9% of the overall sample and 11.9% of women with GDM), GDM status during the index pregnancy was verified by review of medical records.

To reduce the possibility that women in the NW and OB groups had an underlying degree of glucose intolerance that was not detected during the index pregnancy, women meeting the criteria for these groups were excluded if diagnosed with glycosuria, preeclampsia, hypertension, or impaired glucose tolerance during the index pregnancy, or type 2 diabetes in the years since the index pregnancy. It was not feasible to use the same criteria to limit eligibility for the GDM group, however, because of the greater prevalence of these complications among women with GDM. Singletons born at >36 weeks' gestation were eligible. Children were excluded if growth restricted in utero, or had been diagnosed with type 1 diabetes, congenital heart disease, or other significant medical conditions that could impact growth and metabolic health, or had a developmental or cognitive disability that would prevent completion of study procedures. The Institutional Review Board for Human Use at the University of Alabama at Birmingham (UAB) approved all procedures.

2.2 | Procedure

Participants arrived at the research clinic between 8 and 10 AM following a 10 h overnight fast. After informed consent was obtained (and assent of children aged ≥7 years), a fasting blood draw and measurements of anthropometrics and blood pressure were obtained. Children aged ≥7 years underwent a brief physical exam by a licensed nurse practitioner to assess pubertal stage.[23,24] Surveys were administered to assess maternal demographics (education, marital status, race, ethnicity, etc.), household size and income, breastfeeding history, and height and weight at entry to prenatal care for the index pregnancy (if not previously obtained from medical records). Accelerometers were used to assess physical activity, and energy intake was assessed by three 24 h food recalls. Along with maternal height and weight at entry to prenatal care for the index pregnancy, GDM status, gestational age at delivery, and infant birth weight and length, were retrieved from prenatal care and delivery records. For women who delivered outside of UAB, these data were obtained via self-report when incomplete medical records were provided.

2.3 | Anthropometrics

Weight and height were measured using a digital stadiometer (Solo Detecto Eye-Level Physicians Scale, Webb City. MO). Waist and hip circumference were measured with a flexible tape measure (Gulick II Plus model 67,019; FitnessMart Division of Country technology, Inc.; Gays Mills, WI). Thigh, triceps, subscapular, and suprailiac skinfolds were measured with calipers (Lange Skinfold Calipers, Beta Technology Incorporated; Cambridge, MD). Current BMI z-score for children was derived using Centers for Disease

Control and Prevention reference data,[25] and current percent body fat of mothers and children were calculated using established equations.[26,27]

2.4 | Blood pressure

Blood pressure was measured with a digital sphygmomanometer (Spot Vital Signs LXi Device; Welch Allyn; Skaneateles Falls, NY) and adult or pediatric cuffs (Welch Allyn; Skaneateles, NY). Child blood pressure was converted to percentiles based on the sex and height of each child, using American Academy of Pediatrics reference data.[28]

2.5 | Blood draw

After verbal confirmation of a minimum 10 h overnight fast, a blood sample was drawn, processed for serum, and stored at −80C prior to assay. The blood draw was rescheduled if participants had not fasted.

2.6 | Energy intake

Three 24 h dietary recalls were collected and analyzed for mothers and children using the Automated Self-Administered 24 h Dietary Assessment Tool (ASA24, version 2016; National Cancer Institute, Bethesda, MD).[29] A trained research assistant administered two recalls during the clinic visits and one by telephone during the interim week. Mothers were permitted to assist with the child's recall as needed. Total energy intake (kcals per day) per participant was derived from the average of all complete recalls.

2.7 | Physical activity

Women and children wore triaxial accelerometers (wGT3X-BT; ActiGraph Corp., Pensacola FL) around the waist above the right hip for 1 week. Data were analyzed using manufacturer software (ActiLife v6.13.3; ActiGraph Corp., Pensacola FL) and adult or child cut-points were used as appropriate to derive percent time at each intensity of activity.[30,31] Data from the first and last days of use were excluded because they were incomplete days, and any other day with <8 h of wear time was also excluded. Moderate, vigorous and very vigorous activity was summed and averaged across valid days (up to the first 7 days) to derive the percent time in moderate-vigorous physical activity.

2.8 | Assays

Assays were conducted by the Metabolism Core laboratory at UAB. HbA1c was measured in whole blood (Siemens DCA Vantage Analyzer, Deerfield, IL). Fasting glucose, triglycerides, total cholesterol, HDL-C, and CRP were measured on a Stanbio Sirus analyzer (Stanbio Laboratory, Boerne, TX). Intra-assay and inter-assay coefficients of variation (CV) were 1.28% and 4.48% for glucose, 1.11% and 4.28% for triglycerides, 1.33% and 4.28% for total cholesterol, 6.1% and 6.57% for HDL-C, and 7.49% and 5.33% for CRP. Fasting insulin was measured using the TOSOH Bioscience AIA-900 (South San Francisco, CA) and had a mean intra- and inter-assay CV of 1.49% and 3.95%, respectively. Leptin and adiponectin were measured using Millipore Human RIA kits (Millipore Sigma, Billerica, MA), and the intra- and inter-assay CVs for leptin were 5.96% and 0.1%, respectively, and for adiponectin, 4.6% and 8.02%, respectively. Cytokines were measured in duplicate using Mesoscale Discovery Human V-Plex Proinflammatory Panel I kits (Meso Scale Diagnostics, Rockville, MD). The mean intra- and inter-assay CVs were 6.18% and 5.17% for IL6, and 2.26% and 2.69% for TNFα, respectively. Minimum sensitivities for glucose, triglycerides, total cholesterol, CRP, insulin, HDL-C, leptin, adiponectin, IL-6, and TNFα were 2 mg/dl, 2 mg/dl, 5 mg/dl, 0.5 mg/L, 0.5 µU/ml, 5 mg/dl, 0.3 ng/ml, 1.8 µg/ml, 0.1 pg/ml, and 0.1 pg/ml, respectively.

2.9 | Statistical analysis

Descriptive statistics are presented as means and standard deviations for continuous variables and percentages for categorical variables. The distribution of maternal race, ethnicity, marital status, employment status, education level, household income, breastfeeding history, child sex, and child Tanner stage was compared across groups using Fisher's Exact Tests. Analyses of covariance (ANCOVA) were used to explore group differences in current body composition outcomes including BMI of mothers, BMI z-score of children, sum of skinfolds, and % body fat, after adjusting for race, age, household income, energy intake, and % time in moderate-vigorous physical activity. If models were statistically significant, Tukey post hoc tests were used to identify which of the three groups were significantly different from each other. ANCOVA with Tukey post hoc tests were also used to evaluate group differences in current fat distribution (waist to hip ratio) after adjusting for race and age. Models for children were also adjusted for sex and Tanner stage. All serum hormones were log-transformed prior to analysis, and ANCOVA with Tukey post hoc tests as appropriate, were used to test for between group differences in biomarkers and blood pressure. Models for blood pressure and biomarkers were adjusted for covariates selected a priori: race, age, and current % body fat. Current % body fat was included as a covariate in these models to investigate whether any group differences in blood pressure and biomarkers were simply attributable to greater current adiposity in the OB or OB-GDM groups. Tanner stage was added as a covariate in models for children. To investigate whether current adiposity and biomarkers of children were correlated with those of mothers, simple Pearson correlations were calculated for the entire sample and then within each group. The pairwise correlation coefficients in each group

TABLE 1 Characteristics of the mothers and children in the sample (data are mean ± SD unless noted)

	NW	OB	OB-GDM	Overall p-value
Number of mother-child dyads (N)	76	76	67	
BMI at first prenatal visit (kg/m^2)	22.09 ± 1.65^A	**34.93 ± 5.19^B**	**37.45 ± 9.11^C**	**<0.0001**
Maternal ethnicity (%)				0.303
Hispanic or Latino	1.32%	---	2.99%	
Not Hispanic or Latino	97.37%	100.00%	97.01%	
Unknown or not available	1.32%	---	---	
Maternal race (%)				**0.007**
American Indian	1.32%	---	---	
Asian	---	---	1.49%	
Black or African American	78.95%^{A}	**94.75%^{B}**	92.54%^{AB}	
White	19.74%^{A}	**5.26%^{B}**	5.97%^{AB}	
Marital status (% married)	35.53%	27.63%	29.85%	0.573
Maternal education				0.353
Less than high school	1.32%	1.32%	1.49%	
Some high school, didn't graduate	5.26%	5.26%	10.45%	
High school graduate (or GED)	38.16%	43.42%	26.87%	
Some college	28.95%	26.32%	31.34%	
College graduate	11.84%	14.47%	23.88%	
Graduate degree	14.47%	9.21%	5.97%	
Maternal employment outside home (%)	63.16%	72.37%	68.66%	0.483
Household income (%)				0.452
Less than $25k	47.37%	48.68%	47.76%	
$25–34,999k	21.05%	23.68%	22.39%	
$35–49,999k	5.26%	13.16%	11.94%	
$50–74,999k	6.58%	1.32%	7.46%	
$75–99,999k	7.89%	5.26%	5.97%	
$100–149,999k	2.63%	1.32%	2.99%	
$150k or more	7.89%	2.63%	1.49%	
Unknown or not available	1.32%	3.95%	---	
Current age of mothers (years)	32.22 ± 5.26^A	33.00 ± 4.46^A	**35.60 ± 5.02^B**	**<0.001**
Energy intake of mothers (kcals/day)	1956.04 ± 687.56	1718.57 ± 629.61	1907.14 ± 587.17	0.057
Maternal moderate-vigorous physical activity (% time)[a]	2.01 ± 2.26^A	**1.39 ± 1.60^B**	**1.23 ± 1.43^B**	**0.034**
Child sex (% female)	55.26%	50.00%	58.21%	0.617
Child Tanner stage (%)[b]				0.379
Stage 1	88.00%	91.89%	82.09%	
Stage 2	10.67%	5.41%	14.93%	
Stage 3 or more	1.33%	1.35%	2.99%	
Unknown or not available	---	1.35%	---	
Child birthweight (kg)[c]	3.19 ± 0.43^A	3.23 ± 0.46^A	**3.42 ± 0.56^B**	**0.011**
Child age (years)	7.12 ± 1.94	7.19 ± 2.07	6.48 ± 2.13	0.081

(Continues)

T A B L E 1 (Continued)

	NW	OB	OB-GDM	Overall *p*-value
Energy intake of children (kcals/day)	1631.85 ± 416.50	1559.79 ± 448.89	1653.57 ± 596.54	0.480
Child moderate-vigorous physical activity (% time)[d]	4.95 ± 2.79	4.28 ± 2.72	4.35 ± 2.41	0.269

Note: A, B, C Groups with different superscript letters are statistically different from each other. Bold numbers represent groups that are different from the NW (referent) group.
[a]Data from *n* = 65 NW, *n* = 69 OB, and *n* = 63 OB-GDM.
[b]Data from *n* = 75 NW, *n* = 74 OB, and *n* = 67 OB-GDM.
[c]Data from *n* = 75 NW, *n* = 75 OB, and *n* = 67 OB-GDM.
[d]Data from *n* = 67 NW, *n* = 69 OB, and *n* = 62 OB-GDM.

were transformed to z-scores using a Fisher r to z transformation to compare the strength of the mother-child associations across groups. Z-scores were compared using the formula: $Z_{observed} = (z_1 - z_2)/(\text{square root of } [(1/N_1 - 3) + (1/N_2 - 3)])$. Alpha was set at 0.05 for statistical significance, and analyses were performed using SAS (version 9.4; Cary, NC) or R (version 4.0.3).

3 | RESULTS

Two hundred and twenty-one mother-child dyads were enrolled. Data from two dyads were excluded from analyses because delivery records revealed that the child had in utero growth restriction, which was not reported during screening. Consequently, the final sample of $N = 219$ dyads was used in the analyses (NW = 76 OB = 76 GDM = 67).

3.1 | Descriptive characteristics of the dyads

Table 1 displays characteristics of the study sample. Significant between group differences in maternal race, current age, BMI at the first prenatal visit and % time in moderate-vigorous physical activity were observed. The majority of women were non-Hispanic black (88.6%), with more white dyads in the NW group and more black dyads in the OB group ($p < 0.01$); the race distribution in the OB-GDM group was not different from the other two groups. On average, women in the OB-GDM group were older than women in the NW or OB groups ($p < 0.01$). Women in the OB and OB-GDM groups spent less % time in moderate-vigorous physical activity than those in the NW group ($p < 0.05$). By design, there were no women with type 2 diabetes in the NW and OB groups, whereas 20.9% (n = 14) of those in the OB-GDM group had been diagnosed with type 2 diabetes prior to enrollment in this study.

The majority of children in this sample (87.5%) were at Tanner stage 1 (i.e. prepubertal), and 54.3% were female. Birthweight was retrieved from medical records for 92.6% of the children and reported by mothers for the remaining 7.4%. Children in the OB-GDM group were heavier at birth as compared to children in the NW and OB groups ($p < 0.05$), and were slightly, but not significantly, younger at the time of the current study.

3.2 | Mothers' current body composition and cardiometabolic health

Maternal body composition outcomes 4–10 years after the index pregnancy are displayed in Table 2 (unadjusted) and in Figure 1 (adjusted models). In the unadjusted models, significant between group differences were observed for current BMI, sum of skinfolds, % body fat, and the waist-to-hip ratio. After adjusting for race, age, household income, energy intake and % time in moderate-vigorous physical activity, the group differences in current BMI, sum of skinfolds, and % body fat remained ($p < 0.0001$; Figure 1 A-C), with post hoc analyses revealing that the OB and OB-GDM groups did not differ from each other, but had greater current BMI, sum of skinfolds and % body fat than the NW group. Current waist-to-hip ratio was greater in the OB-GDM group as compared to the NW ($p < 0.0001$) and OB groups ($p = 0.02$; Figure 1D), after adjusting for race and age.

Maternal blood pressure and biomarkers are displayed in Table 2 (unadjusted) and Table 3 (adjusted). In unadjusted models, significant group differences were observed for all outcomes except FFA and total cholesterol. Post hoc analyses showed that as compared to the NW group, women in the OB and OB-GDM groups had higher blood pressure, triglycerides, insulin, HOMA-IR, leptin, leptin:adiponectin ratio, CRP and IL6, and lower HDL-C and adiponectin than the NW group. The OB-GDM group also had higher HbA1c, fasting glucose, and TNFα than the NW group. After adjusting for age, race and current % body fat (Table 4), HbA1c, fasting glucose, HOMA-IR, and triglycerides remained higher in the OB-GDM group compared to the NW and OB groups ($p < 0.05$). HDL-C and adiponectin remained lower, and CRP and IL6 remained higher, in the OB-GDM versus NW group, after adjusting for age, race, and current % body fat. Importantly, most differences between the NW and OB groups observed in the unadjusted models diminished after adjusting for current % body fat, aside from HDL-C which remained lower in the OB compared to NW group ($p < 0.05$).

TABLE 2 Group difference in **mothers'** current body composition and cardiometabolic biomarkers 4–10 years after pregnancy

	NW	OB	OB-GDM	Overall model p-value
Current BMI (kg/m^2)	24.95 ± 3.99[A]	**38.13 ± 7.41**[B]	**38.76 ± 8.87**[B]	**<0.001**
Sum of skinfolds (mm)	107.33 ± 35.68[A]	**159.94 ± 38.14**[B]	**163.78 ± 37.03**[B]	**<0.001**
Total body fat (%)	32.02 ± 7.34[A]	**42.13 ± 5.89**[B]	**42.87 ± 5.81**[B]	**<0.001**
Waist-to-hip ratio	0.80 ± 0.06[A]	**0.85 ± 0.10**[B]	**0.89 ± 0.08**[C]	**<0.001**
Systolic blood pressure (mm Hg)	115.30 ± 13.04[A]	118.28 ± 13.51[AB]	**122.26 ± 15.15**[B]	**<0.05**
Diastolic blood pressure (mm Hg)	75.17 ± 8.32[A]	**78.76 ± 7.74**[B]	**80.38 ± 6.95**[B]	**<0.001**
HbA1c (%)	5.41 ± 0.65[A]	5.72 ± 1.04[A]	**6.57 ± 1.86**[B]	**<0.001**
Fasting glucose (mg/dl)	90.42 ± 8.99[A]	93.20 ± 25.05[A]	**120.41 ± 67.01**[B]	**<0.001**
Triglycerides (mg/dl)	66.24 ± 34.14[A]	**78.24 ± 30.63**[B]	**105.99 ± 86.12**[C]	**<0.001**
Fasting insulin (µU/ml)	9.09 ± 7.93[A]	**15.38 ± 11.45**[B]	**17.40 ± 11.62**[B]	**<0.001**
HOMA-IR	2.11 ± 2.10[C]	**3.50 ± 2.67**[B]	**5.30 ± 4.77**[C]	**<0.001**
FFA (mEq/L)	0.70 ± 0.36	0.65 ± 0.35	0.66 ± 0.40	0.57
Total cholesterol (mg/dl)	173.12 ± 36.63	176.81 ± 35.91	180.89 ± 46.90	0.60
HDL-C (mg/dl)	67.97 ± 12.94[A]	**59.20 ± 9.94**[B]	**56.19 ± 11.91**[B]	**<0.001**
Leptin (ng/ml)	37.40 ± 34.69[A]	**80.13 ± 31.27**[B]	**72.67 ± 33.35**[B]	**<0.001**
Adiponectin (µg/ml)	12.31 ± 6.06[A]	**8.23 ± 4.03**[B]	**6.71 ± 3.44**[C]	**<0.001**
Leptin: Adiponectin ratio	4.65 ± 6.87[A]	**12.63 ± 8.26**[B]	**13.73 ± 9.67**[B]	**<0.001**
CRP (mg/L)	1.73 ± 2.47[A]	**7.24 ± 9.41**[B]	**10.74 ± 12.24**[C]	**<0.001**
IL6[a] (pg/ml)	0.67 ± 0.48[A]	**1.35 ± 0.89**[B]	**1.56 ± 1.21**[B]	**<0.001**
TNFα (pg/ml)	2.24 ± 1.88[A]	2.23 ± 0.47[AB]	**2.49 ± 0.80**[B]	**<0.05**

Note: Data are unadjusted mean ± standard deviation. Analyses were completed on $N = 76, 76, 67$ women in each group, respectively, for the body composition measures, and $N = 76, 75, 67$ in each group for serum outcomes (missing serum for one woman), unless noted. [A, B, C]: Different superscript letters denote statistically significant group means. Bold numbers represent groups that are significantly different than the NW group.

Abbreviations: BMI, body mass index; CRP, C-Reactive Protein; FFA, Free Fatty Acids; HbA1c, hemoglobin A1c; HDL-C, High Density Lipoprotein - Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin 6; TNFα, Tumor Necrosis Factor alpha.

[a]IL6: Removed n = 2 from OB for IL6 outliers (>16 pg/ml).

3.3 | Children's body composition and cardiometabolic health

Children's body composition outcomes are shown in Table 4 (unadjusted) and Figure 2 (adjusted). In unadjusted models, group differences were observed for current BMIz, % body fat, and waist-to-hip ratio, and these differences remained after adjusting for covariates (Figure 2A,C and D). In post hoc analyses, current BMIz was higher for children in the OB-GDM and OB groups as compared to the NW group ($p < 0.05$), and current % body fat and waist-to-hip ratio were higher in the OB-GDM group compared to the NW, but not OB, group ($p < 0.05$).

As shown in Table 4 (unadjusted) and Table 5 (adjusted), children's blood pressure and cardiometabolic biomarkers were similar across groups, with only diastolic blood pressure percentile differing by group. After adjusting for race, Tanner stage, and current % body fat, the model for diastolic blood pressure percentile remained statistically significant ($p < 0.05$), but post hoc analyses between groups did not attain statistical significance. There was a trend for a

difference in FFA ($p = 0.051$), with lower FFA in the OB and OB-GDM groups compared to the NW group, but post hoc analyses failed to attain statistical significance.

3.4 | Mother-child correlations

Simple Pearson correlations were calculated to explore associations among mother and child body composition and cardiometabolic health outcomes. In the overall group, positive correlations were observed for all body composition measures obtained at the time of the study: maternal BMI × child BMIz ($r = 0.264$, $p < 0.0001$), mother × child sum of skinfolds ($r = 0.333$, $p < 0.0001$), mother × child % body fat ($r = 0.292$, $p < 0.0001$), and mother × child waist-to-hip ratio ($r = 0.263$, $p < 0.0001$). Within each group (Figure 3), the sum of skinfolds was the only body composition measure that was significantly and positively correlated in all three groups (Figure 3B, $p < 0.05$), although a similar pattern was observed for current % body fat
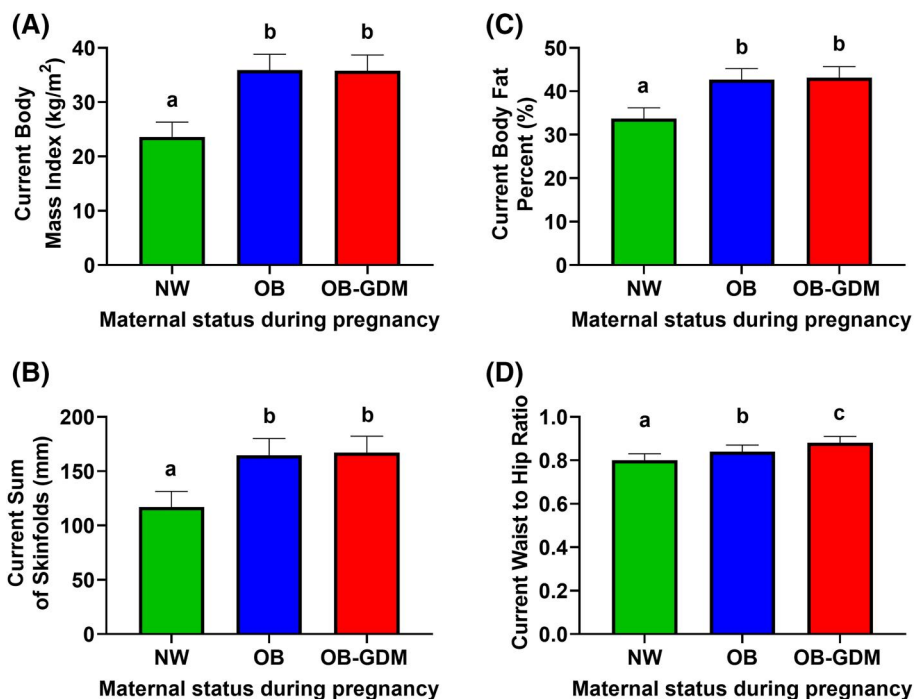
FIGURE 1 Mother's current (A) BMI, (B) sum of skinfolds, (C) % body fat were adjusted for age, race, income, energy intake, and % time in moderate-vigorous physical activity. Mother's (D) current waist-to-hip ratio was adjusted for race and age. Groups with different letters are significantly different from each other ($p < 0.05$)

TABLE 3 Group difference in **mothers'** cardiometabolic biomarkers 4–10 years after pregnancy. Data are mean $\pm$ SEM, adjusted for age, race, and current %fat

	NW	OB	OB-GDM	Overall model *p*-value
	76	75	67	
Systolic blood pressure (mm Hg)	115.87 $\pm$ 5.06	115.87 $\pm$ 5.23	119.127 $\pm$ 5.20	0.31
Diastolic blood pressure (mm Hg)	76.40 $\pm$ 2.81	77.67 $\pm$ 2.91	78.90 $\pm$ 2.89	0.29
HbA1c (%)	5.18 $\pm$ 0.47[A]	5.14 $\pm$ 0.49[A]	**5.99 $\pm$ 0.49[B]**	**<0.001**
Fasting glucose (mg/dl)[a]	90.09 $\pm$ 15.22[A]	85.29 $\pm$ 15.72[A]	**112.61 $\pm$ 15.62[B]**	**<0.001**
Fasting insulin (µU/ml)[a]	11.29 $\pm$ 3.77	13.38 $\pm$ 3.90	16.27 $\pm$ 3.87	0.06
HOMA-IR[a]	2.60 $\pm$ 1.22[A]	2.79 $\pm$ 1.26[A]	**4.83 $\pm$ 1.26[B]**	**<0.001**
Triglycerides (mg/dl)[a]	105.43 $\pm$ 20.63[A]	105.81 $\pm$ 21.32[A]	**132.10 $\pm$ 21.18[B]**	**<0.05**
HDL-C (mg/dl)[a]	63.60 $\pm$ 4.23[A]	**56.68 $\pm$ 4.37[B]**	**52.32 $\pm$ 4.34[B]**	**<0.0001**
Total cholesterol (mg/dl)[a]	163.97 $\pm$ 14.74	158.34 $\pm$ 15.24	159.43 $\pm$ 15.14	0.77
Adiponectin (µg/ml)[a]	10.53 $\pm$ 1.61[A]	8.68 $\pm$ 1.66[AB]	**6.89 $\pm$ 1.65[B]**	**<0.001**
Leptin (ng/ml)[a]	45.11 $\pm$ 10.30	57.11 $\pm$ 10.64	51.30 $\pm$ 10.57	0.09
Leptin-to-adiponectin ratio[a]	6.76 $\pm$ 2.77	8.50 $\pm$ 2.86	9.89 $\pm$ 2.84	0.14
FFA (mEq/L)[a]	0.68 $\pm$ 0.14	0.57 $\pm$ 0.14	0.55 $\pm$ 0.14	0.23
CRP (mg/L)[a]	4.10 $\pm$ 3.25[A]	5.97 $\pm$ 3.36[AB]	**8.94 $\pm$ 3.34[B]**	**<0.05**
IL6 (pg/ml)[b]	0.67 $\pm$ 0.33[A]	1.07 $\pm$ 0.34[AB]	**1.33 $\pm$ 0.34[B]**	**<0.01**
TNFa (pg/ml)[a]	2.57 $\pm$ 0.46	2.45 $\pm$ 0.47	2.71 $\pm$ 0.47	0.49

Note: [A, B]: Groups with the different superscript letters are significantly different from each other, $p < 0.05$. Bold numbers represent groups that are different from the NW group.

Abbreviations: CRP, C-Reactive Protein; FFA, Free Fatty Acids; HDL-C, High Density Lipoprotein - Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin 6; TNFα, Tumor Necrosis Factor alpha.

[a]Data from n = 76 NW, n = 75 OB, n = 67 OB-GDM.

[b]Data from n = 76 NW, n = 72 OB, n = 67 OB-GDM.

T A B L E 4 Group difference in **children's** body composition and cardiometabolic biomarkers at 4–10 years of age. Data are unadjusted mean ± standard deviation.

	NW	OB	OB-GDM	Overall model p-value
BMIz	0.18 ± 1.30[A]	**0.76 ± 1.11[B]**	**0.98 ± 1.33[B]**	**<0.01**
Sum of skinfolds (mm)	58.06 ± 36.80	66.41 ± 40.02	72.10 ± 40.63	0.10
Total body fat (%)	22.60 ± 9.50[A]	25.50 ± 9.95[AB]	**26.71 ± 9.66[B]**	**<0.05**
Waist to hip ratio	0.85 ± 0.05[A]	0.86 ± 0.55[AB]	**0.87 ± 0.06[B]**	**<0.05**
Systolic blood pressure percentile[a]	69.36 ± 20.46	70.75 ± 25.40	75.74 ± 22.84	0.22
Diastolic blood pressure percentile[a]	72.93 ± 20.69[A]	75.45 ± 20.48[AB]	**81.39 ± 14.94[B]**	**<0.05**
HbA1c (%)	5.40 ± 0.30	5.44 ± 0.33	5.45 ± 0.37	0.67
Fasting glucose (mg/dl)	88.19 ± 8.48	87.77 ± 9.50	88.60 ± 6.78	0.85
Triglycerides (mg/dl)	60.17 ± 24.85	62.31 ± 28.98	62.92 ± 26.43	0.83
Fasting insulin (μU/ml)	7.54 ± 10.15	10.01 ± 12.80	7.85 ± 7.87	0.35
HOMA-IR	1.73 ± 2.52	2.25 ± 3.10	1.77 ± 1.85	0.38
FFA (mEq/L)	0.94 ± 0.46	0.77 ± 0.35	0.82 ± 0.39	0.35
Total cholesterol (mg/dl)	162.92 ± 30.98	157.41 ± 29.81	162.48 ± 33.26	0.55
HDL-C (mg/dl)	64.10 ± 11.85	63.97 ± 12.59	64.44 ± 11.18	0.97
Leptin (ng/ml)	13.20 ± 16.72	16.70 ± 19.06	17.04 ± 16.79	0.39
Adiponectin[b] (μg/ml)	15.22 ± 5.54	13.30 ± 5.73	14.52 ± 6.44	0.18
Leptin: Adiponectin ratio[b]	1.10 ± 1.59	1.83 ± 2.77	1.66 ± 2.51	0.19
CRP (mg/L)	1.51 ± 3.57	1.14 ± 1.75	1.95 ± 3.46	0.32
IL6 (pg/ml)	0.65 ± 0.88	0.68 ± 0.78	0.70 ± 0.89	0.94
TNFα (pg/ml)	3.38 ± 0.91	3.35 ± 0.86	3.70 ± 1.11	0.09

Note: Analyses were completed on N = 76, 76, 67 children in each group for the body composition measures, and N = 63, 64, 63 children in each group for serum outcomes, unless noted. [A, B]: Different superscript letters denote statistically significant group means. Bold numbers represent groups that are significantly different than the NW group.

Abbreviations: BMI, body mass index; CRP, C-Reactive Protein; FFA, Free Fatty Acids; HbA1c, hemoglobin A1c; HDL-C, High Density Lipoprotein - Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin 6; TNFα, Tumor Necrosis Factor alpha.

[a]Data for 73, 74, 66; age removed from models as it was included in the percentile calculation.

[b]Data for 63 per group.

(Figure 3C). The magnitude of mother-child correlations did not differ across groups.

Table 6 shows the correlation coefficients for mother-child blood pressure and biomarkers across the whole sample combined and within each of the three groups. When groups were combined, modest correlations were observed for systolic blood pressure and all biomarkers except fasting glucose, HOMA-IR, CRP and IL6 (r = 0.17–0.31, p < 0.05). When split into groups, HDL-C was the only outcome that was significantly correlated in all three groups and the strength of this association did not differ across groups. Dyads in the OB group were more similar than those in the other two groups, with all outcomes except diastolic blood pressure and IL6 being positively associated among mothers and children (r = 0.26–0.52, p < 0.05). Further, the association between mother and child leptin:adiponectin ratio, CRP, and TNFα was significantly greater in the OB group versus the NW group.

4 | DISCUSSION

The objective of this study was to comprehensively and concurrently compare body composition and cardiometabolic health of women and children 4–10 years after a pregnancy complicated by maternal overweight/obesity and GDM (OB-GDM), maternal overweight/obesity without GDM (OB), and compared to mother-child dyads for which women had normal weight without GDM during pregnancy (NW; healthy referent group). Women in the OB-GDM group had greater central adiposity 4–10 years after pregnancy, and poorer cardiometabolic outcomes independent of current adiposity, compared to NW and OB groups. In contrast, poorer indices of cardiometabolic health for women in the OB compared to the NW group diminished after adjusting for current adiposity. Children's body composition outcomes were similar to mothers, with those exposed in utero to OB-GDM having the highest total and central adiposity, each of which was significantly greater than for children born to
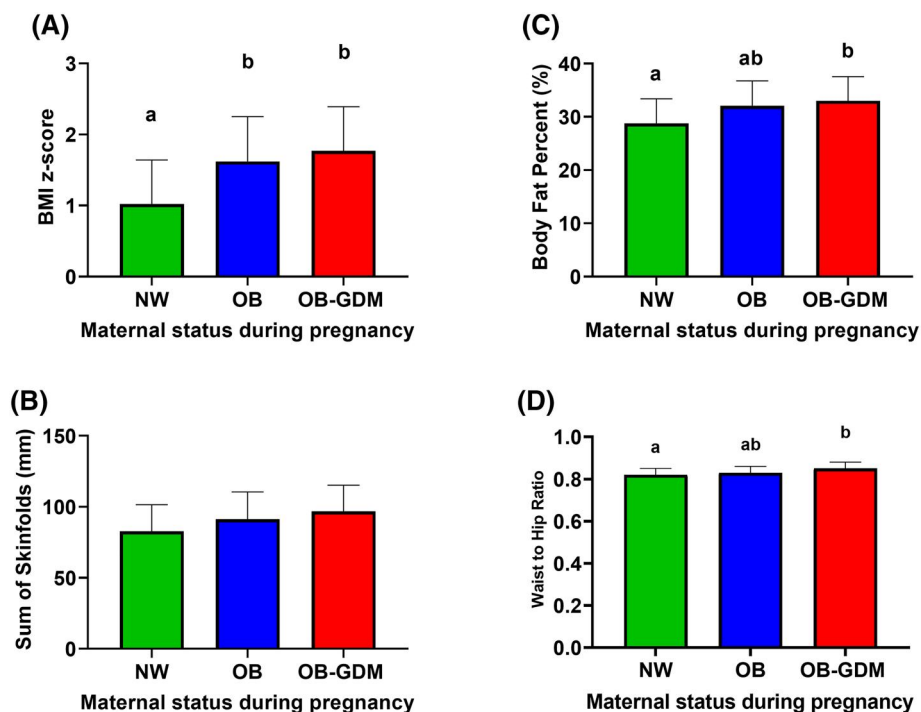
FIGURE 2 Children's current (A) BMI z-score, adjusted for race, tanner, income, energy intake, and % time in moderate-vigorous physical activity, (B) sum of skinfolds, adjusted for age, race, sex, Tanner, household income, energy intake, and % time in moderate-vigorous physical activity, (C) % body fat, adjusted for age, Tanner, household income, energy intake, and % time in moderate-vigorous physical activity, and (D) waist-to-hip ratio, adjusted for race, Tanner, and child sex. Groups with different letters are significantly different from each other ($p < 0.05$)

women with NW. Despite group differences in adiposity of children, diastolic blood pressure percentile was the only cardiometabolic outcome that differed across groups, trending higher for those in the OB-GDM group.

A key finding in this study was that, after adjusting for current adiposity, women with OB-GDM still had higher HbA1c, glucose, triglycerides and HOMA-IR, compared to women with OB or NW during pregnancy, whereas for women in the OB group, most of the cardiometabolic outcomes that differed from the NW group were no longer different after adjusting for current adiposity. The only difference that remained between the OB and NW groups after adjusting for current adiposity was lower HDL-C concentrations in the OB group. Poorer outcomes among women with OB-GDM are consistent with previous research showing that women with prior GDM have more insulin resistance, greater risk for type 2 diabetes, and dyslipidemia, compared to women without prior GDM,[16,17,32-34] and suggest that underlying deficits in glucose metabolism exist independent of current adiposity for women with prior GDM. In contrast, the fact that most differences between the OB and NW groups were abolished after adjusting for current adiposity suggests that poorer cardiometabolic outcomes in women with a history of uncomplicated obesity in pregnancy are secondary to excess body fat.

Children exhibited similar group differences in body composition as the mothers. Specifically, current BMIz was greater in children from the OB and OB-GDM groups, and the OB-GDM group also had

greater total body fat % and waist-to-hip ratio than the NW group. Greater total and central adiposity among children exposed to GDM is consistent with prior research,[35-38] and is notable because of the well-known association between central adiposity and insulin resistance. Prior research has shown that by early to mid- adolescence, teens exposed to GDM in utero exhibit phenotypes consistent with greater risk for type 2 diabetes, including more insulin resistance and lower glucose tolerance as compared to teens born to non-GDM mothers.[13,16,17] In the current study, however, no other group differences in cardiometabolic outcomes were observed in the unadjusted or adjusted models. It is possible therefore, that the development of insulin resistance, glucose intolerance, and dyslipidemia among OB-GDM offspring is temporally dissociated from differences in the pattern of fat accrual, and will emerge during the adolescent years.

We also investigated the magnitude of association between outcomes in mothers and children. Overall, current maternal BMI and adiposity were positively, but modestly, correlated with children's BMIz and adiposity. These results are consistent with prior research reporting heritability of somatotype.[39-42] When separated by group, the correlation of mother and child sum of skinfolds was significant for all three groups, suggesting that the capacity to expand subcutaneous fat may be similar between mothers and children, at least during the prepubertal years. This conclusion is supported by a previous study of twins in which 50%–70% of the variability in endomorphy, the somatotype component that reflects subcutaneous

TABLE 5 Group difference in **children's** cardiometabolic biomarkers at 4–10 years of age. Data are mean ± SEM, adjusted for age, race, %fat, and Tanner stage

	NW	OB	OB-GDM	Overall model p-value
	74	73	64	
Systolic blood pressure percentile[a]	45.16 ± 11.11	44.35 ± 11.00	50.34 ± 10.87	0.29
Diastolic blood pressure percentile[a]	60.29 ± 9.37	60.73 ± 9.60	68.31 ± 9.39	**0.04**
HbA1c (%)[b]	5.42 ± 0.16	5.38 ± 0.17	5.43 ± 0.15	0.69
Fasting glucose (mg/dl)[c]	84.65 ± 4.16	83.17 ± 4.28	84.62 ± 4.10	0.57
Triglycerides (mg/dl)[c]	69.04 ± 12.54	68.37 ± 12.94	67.80 ± 12.38	0.97
Fasting insulin (μU/ml)[c]	8.26 ± 4.30	9.27 ± 4.43	7.51 ± 4.24	0.57
HOMA-IR[c]	1.59 ± 1.06	1.75 ± 1.10	1.37 ± 1.05	0.65
FFA (mEq/L)	0.83 ± 0.20	0.65 ± 0.21	0.69 ± 0.20	0.051
Total cholesterol (mg/dl)[c]	132.31 ± 15.37	123.64 ± 15.85	131.54 ± 15.16	0.26
HDL-C (mg/dl)[c]	58.67 ± 6.01	58.96 ± 6.19	60.09 ± 5.93	0.82
Leptin (ng/ml)[d]	16.98 ± 4.34	17.13 ± 4.48	19.61 ± 4.29	0.22
Adiponectin (μg/ml)[c]	12.46 ± 2.94	11.36 ± 3.03	11.97 ± 2.90	0.61
Leptin: Adiponectin ratio[d]	2.91 ± 0.66	3.14 ± 0.68	3.25 ± 0.65	0.40
CRP (mg/L)[c]	2.46 ± 1.52	1.69 ± 1.57	2.60 ± 1.50	0.25
IL6 (pg/ml)[d]	0.56 ± 0.42	0.53 ± 0.43	0.50 ± 0.41	0.93
TNFa (pg/ml)[d]	4.15 ± 0.44	4.14 ± 0.45	4.23 ± 0.43	0.85

Abbreviations: CRP, C-Reactive Protein; FFA, Free Fatty Acids; HDL-C, High Density Lipoprotein–Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin 6; TNFα, Tumor Necrosis Factor alpha.

[a]age removed from models as it was included in the percentile calculation.

[b]Data from $n = 60$ NW, $n = 61$ OB, $n = 55$ OB-GDM.

[c]Data from $n = 61$ NW, $n = 61$ OB, $n = 56$ OB-GDM.

[d]Data from $n = 61$ NW, $n = 60$ OB, $n = 56$ OB-GDM.

fat, is attributable to shared genotype in children aged 10–13 years, but the genetic contribution declines with age, particularly in boys.[41] Other body composition outcomes were not as well correlated across all groups in the current study, suggesting that factors beyond genotype may contribute to children's BMIz, % body fat, and waist-to-hip ratio.

Modest mother-child correlations were also observed for the indices of cardiometabolic health, and when split into the three groups, associations were stronger for dyads in the OB group compared to the other two groups. Almost all (i.e. 11 of 13) cardiometabolic biomarkers were significantly correlated in the OB group, compared to just three of 13 biomarkers in the NW and GDM groups. The correlation coefficients between mother and child leptin, leptin-to-adiponectin ratio, and inflammatory cytokines were significantly greater in the OB group than in the NW group or the GDM group, suggesting that mother-child dyads with a history of uncomplicated obesity have more similar cardiometabolic health than do dyads characterized by NW or GDM in pregnancy. Reasons for this difference are unclear, but if confirmed in a larger study, it would be interesting to investigate whether the strength of association between mother and child outcomes differs across age or pubertal status.

Strengths of this study include the concurrent and comprehensive assessment of mothers and children 4–10 years after pregnancy characterized by maternal obesity with and without GDM, which was important to dissociate the effect of maternal obesity alone versus obesity _and_ GDM on maternal-child outcomes, and to investigate maternal-child correlations. Direct comparison of OB and OB-GDM groups showed that poorer cardiometabolic outcomes persist independent of current adiposity for women in the OB-GDM group but appear to be secondary to current adiposity in the OB group. For children, although in utero exposure to GDM was associated with greater total and central adiposity, the notable lack of other differences implies that the timeline for disease progression lags behind fat mass accrual. This is important to inform future studies about when to investigate the development of insulin resistance and cardiometabolic disease, and ultimately, when to intervene to optimize cardiometabolic health. This study did not include a NW-GDM group due to the relatively low prevalence of NW among women with GDM, but this precluded the ability to distinguish whether GDM in the absence of overweight/obesity was associated with future cardiometabolic outcomes. A potential selection bias was introduced in this study due to the exclusion of women with type 2 diabetes or a history of preeclampsia or
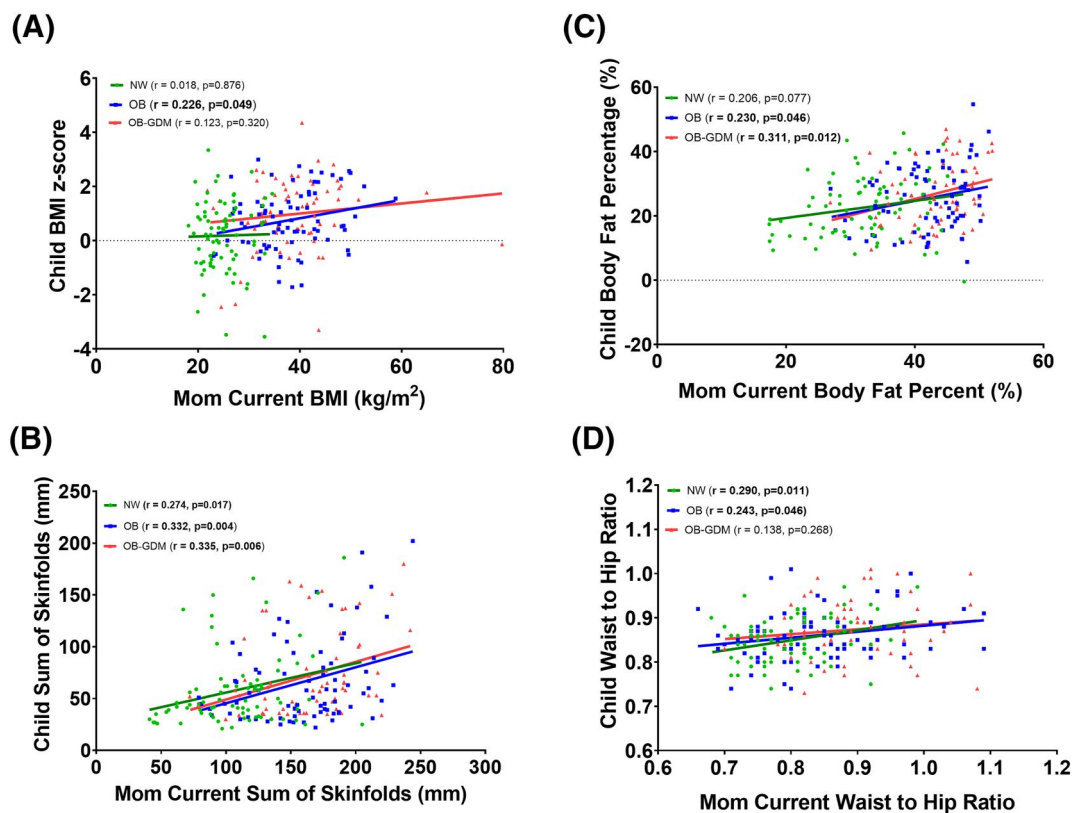
FIGURE 3 Correlations between child and maternal body composition measures. (A), Current BMI (mothers) and BMI z-score (children), (B) current sum of skinfolds for mothers and children, (C) current % body fat for mothers and children, and (D) current waist-to-hip ratio for mothers and children

hypertension from the OB and NW groups but not the OB-GDM group. This selection bias may limit generalizability of these findings, particularly among women with no history of GDM, to those with a relatively healthy and uncomplicated pregnancy history. Relative homogeneity of the sample, with primarily non-Hispanic black participants, also limits generalizability of this study. The cross-sectional design and modest sample size were limitations that prevented characterization of longitudinal changes in cardiometabolic health. Also, given that no data were obtained prior to the index pregnancy, it was not possible to determine whether differences in cardiometabolic health across groups existed prior to pregnancy. Finally, no data were available about the early childhood environment or growth during infancy, which could have impacted children's adiposity and cardiometabolic outcomes.

To conclude, results of this study indicate that women with obesity *and* GDM during an earlier pregnancy have a poor cardiometabolic phenotype that is independent of current adiposity, whereas most cardiometabolic perturbations in women with obesity and no prior GDM are secondary to current adiposity. For children, results suggest that in utero exposure to maternal obesity *and* GDM is associated with greater total and central adiposity, but obesity-related cardiometabolic perturbations may not emerge until children reach puberty or adolescence. Modest correlations between mother and child body composition and cardiometabolic outcomes suggest that even at this young age, children's phenotypes bear some resemblance to those

of mothers, but more research is needed in larger cohorts to fully investigate whether the association of mother-child phenotypes differs across age, sex, and risk for disease. Future research should prospectively compare the trajectory of fat accrual and cardiometabolic outcomes, along with potential genetic and lifestyle contributors, among children born to women with obesity, with and without GDM.

TABLE 6 Correlation of mother blood pressure with child blood pressure percentile, and of mother-child biomarkers 4–10 years after pregnancy

	Overall	NW	OB	OB-GDM
Systolic blood pressure	0.19**	−0.008	0.305**	0.188
Diastolic blood pressure	0.11	0.088	0.106	−0.001
Glucose	0.04	0.170	0.260*	−0.005
Fasting insulin	0.22**	0.245	0.316*	0.007
HOMA-IR	0.14	0.225	0.303*	−0.002
Total cholesterol	0.28***	0.140	0.428***	0.291*
HDL-C	0.31****	0.320*	0.387**	0.302*
Leptin	0.17*	0.280*,a	0.270*a	−0.165b
Adiponectin	0.26***	0.262*	0.369**	0.134
Leptin: Adiponectin ratio	0.18*	0.018a	**0.467***b**	−0.147a
CRP	0.13	0.050a	**0.398**b**	0.051a
IL6	0.11	−0.138a	0.189b	0.096ab
TNFα	0.20**	0.108a	**0.518****b**	0.322*ab

Note: a, b: Groups with different superscript letters have a correlation coefficient that is significantly different from each other. Bold numbers represent groups that have significant correlations, with the strength of the association different than that in the NW group.

Abbreviations: CRP, C-Reactive Protein; FFA, Free Fatty Acids; HDL-C, High Density Lipoprotein–Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin 6; TNFα, Tumor Necrosis Factor alpha.

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; ****p-value < 0.0001.

CONFLICT OF INTEREST

Stella Aslibekyan discloses employment and equity in 23andMe, Inc. She was involved in the design and initiation of this project prior to leaving UAB to join 23andMe, Inc. The other authors and the institution have received grants supporting their work on this project, as described in "Funding". Additional grants and contracts and participation on advisory boards during the last 36 months for work unrelated to this project have been disclosed in the combined COI. All authors report no financial conflicts of interest pertaining to work on this project.

AUTHOR CONTRIBUTIONS

Paula Chandler-Laney, W. Timothy Garvey, Lorie M. Harper and Cora E. Lewis designed this study. Samantha L. Martin and Paula Chandler-Laney wrote the manuscript. Li Zhang and Nengjun Yi developed the data analysis plan and conducted data analyses. Paula Chandler-Laney, Jessica Bahorski, Nefertiti Durant, Lorie M. Harper, Bertha A. Hidalgo, Stella Aslibekyan, Ashley N. Battarbee and Kirk Habegger developed the protocol and provided expert content input. Samantha L. Martin, Makenzie L. Callahan, Jessica Bahorski, Bethany A. Moore and Alysha Everett were involved with data acquisition, processing, and preliminary analyses. Paula Chandler-Laney, Samantha L. Martin, W. Timothy Garvey, Bertha A. Hidalgo, Stella Aslibekyan, Lorie M. Harper, Kirk Habegger, Ashley N. Battarbee, Nefertiti Durant, Rogerio Sertie and Jessica Bahorski contributed to the manuscript review and editing. All authors read and approved the final version of this manuscript. Paula Chandler-Laney takes full responsibility for this work, including the study design, access to data, and decision to submit and publish the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.