Development of Early Adiposity in Infants of Mothers With Gestational Diabetes Mellitus

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OBJECTIVE

Infants born to mothers with gestational diabetes mellitus (GDM) are at greater risk of later adverse metabolic health. We examined plausible candidate mediators, adipose tissue (AT) quantity and distribution and intrahepatocellular lipid (IHCL) content, comparing infants of mothers with GDM and without GDM (control group) over the first 3 postnatal months.

RESEARCH DESIGN AND METHODS

We conducted a prospective longitudinal study using MRI and spectroscopy to quantify whole-body and regional AT volumes, and IHCL content, within 2 weeks and 8–12 weeks after birth. We adjusted for infant size and sex and maternal prepregnancy BMI. Values are reported as the mean difference (95% CI).

RESULTS

We recruited 86 infants (GDM group 42 infants; control group 44 infants). Mothers with GDM had good pregnancy glycemic control. Infants were predominantly breast-fed up to the time of the second assessment (GDM group 71%; control group 74%). Total AT volumes were similar in the GDM group compared with the control group at a median age of 11 days (−28 cm^3 [95% CI −121, 65], $P = 0.55$), but were greater in the GDM group at a median age of 10 weeks (247 cm^3 [56, 439], $P = 0.01$). After adjustment for size, the GDM group had significantly greater total AT volume at 10 weeks than control group infants (16.0% [6.0, 27.1], $P = 0.002$). AT distribution and IHCL content were not significantly different at either time point.

CONCLUSIONS

Adiposity in GDM infants is amplified in early infancy, despite good maternal glycemic control and predominant breast-feeding, suggesting a potential causal pathway to later adverse metabolic health. Reduction in postnatal adiposity may be a therapeutic target to reduce later health risks.

Diabetes in pregnancy is increasing and currently affects up to 5% of women in the U.K. (1) and up to 9.2% in the U.S. (2). Approximately 87.5% of cases are gestational diabetes mellitus (GDM), 7.5% are type 1 diabetes, and 5% are type 2 diabetes (1). The offspring of mothers with diabetes have greater risks of adverse metabolic sequelae in childhood and later life that appear to be additional to genetic predisposition (3–5).

The underlying mechanisms are unclear, but increased infant adiposity is a plausible mediator because adiposity in childhood and adult life are associated with type 2 diabetes and cardiovascular disease (6). The Hyperglycemia and Adverse

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Pregnancy Outcome (HAPO) study identified a strong association between maternal glycemia and anthropometry-derived adiposity in newborn infants (7). The first 3 months of life is a critical period for adipose tissue (AT) deposition (8), but, to our knowledge, longitudinal examination of the quantity and distribution of AT in early infancy has not been undertaken in the offspring of mothers with diabetes.

Internal abdominal AT is associated with higher metabolic risk (9), whereas abdominal or nonabdominal superficial subcutaneous AT may be protective (10). Indirect body composition techniques require assumptions to enable the calculation of fat mass, and although they may provide an indication of fat mass distribution, they are unable to differentiate individual AT compartments.

We aimed to examine total and regional AT volumes using a direct technique, whole-body MRI, soon after birth and again in later infancy, in a prospective cohort of infants of mothers with GDM and control infants. Intrahepatocellular lipid (IHCL) content has a strong association with internal abdominal AT and may be more closely linked with adverse metabolic outcomes (11), and, because nonalcoholic fatty liver disease is now the most common form of chronic liver disease in children (12), we also aimed to compare IHCL content.

RESEARCH DESIGN AND METHODS

We recruited healthy, full-term (37–42 weeks) infants with GDM and control infants from the postnatal wards at Chelsea and Westminster Hospital, London, U.K., between October 2011 and October 2014. This is a major teaching hospital, with ~6,000 births each year. We endeavored to approach all mothers with GDM and similar numbers of control subjects. We used no additional selection criteria, and recruited in keeping with the availability of the MRI scanner. We excluded mothers with preexisting diabetes and small-for-gestational-age infants because we have previously shown them to have altered AT distribution (13). We undertook assessments at the following two time points: within 2 weeks of birth and at 8–12 weeks after birth. If the initial scan was unsuccessful, the infant did not continue in the study. The study received approval from the National Research Ethics Committee (reference 11/LO/1167), and informed, written maternal consent was obtained.

Hospital policy was for all women with risk factors for GDM to undergo a standard 2-h 75-g oral glucose tolerance test at 26 weeks of gestation. If the results were normal, in women with previous GDM this was repeated at 30 weeks. All women without risk factors underwent a 1-h, 50-g glucose screening test at 26–28 weeks of gestation. Those with abnormal screening results ($\geq$7.8 mmol/L) then had a full oral glucose tolerance test. GDM was diagnosed in mothers by the obstetric team using the following criteria: fasting plasma glucose concentration $\geq$5.3 mmol/L or 2-h plasma glucose concentration $\geq$7.8 mmol/L. Women were referred to the antenatal diabetes clinic for dietary and exercise advice, and were requested to monitor premeal and postmeal blood glucose levels. Target blood glucose levels were $<$5.5 mmol/L premeal and $<$7.8 mmol/L 1 h postmeal. Metformin treatment was considered in obese or severely insulin-resistant women, and insulin treatment was commenced if blood glucose levels exceeded target ranges.

We used maternal height recorded at the antenatal booking and prepregnancy weight obtained by maternal recall to calculate the prepregnancy BMI. Recalled and measured prepregnancy weight are highly correlated (14). We measured infant weight, length, and occipital frontal circumference (OFC) at the time of imaging. Weight was obtained using scales (M-300 Portable Baby Scale; Marsden, London, U.K.; precision $\pm$2 g), length was measured using a Rollametre (Raven Equipment Ltd., Dunmow, Essex, U.K.), and OFC was recorded using a tape measure (Child Growth Foundation, London, U.K.).

We classified infant feeding as exclusively or predominantly breast-fed, exclusively or predominantly formula fed, or mixed fed (similar proportions of breast milk and formula). Ethnicity was reported by parents, and was categorized as Asian, Afro-Caribbean, Caucasian, African, and mixed race.

We estimated the sample size for the primary outcome using pilot data and simulation, based on 5% significance, adjusting for infant size, and allowing for the possibility of an interaction between maternal diabetes status and infant sex. We calculated that 42 infants in each group would provide 80% power to detect a mean difference between GDM and control infants of 86 cm^3 (11% difference) in total AT volume and 90% power to detect a difference of 6 cm^3 (38%) in the smallest of the measured regional compartments, the abdominal deep subcutaneous compartment. We considered these differences likely to be clinically relevant because they are similar to that between preterm-at-term and healthy term infants (15), and the former is a group also at risk for later adverse metabolic health. We therefore aimed to continue recruitment until a minimum of 42 infants in each group had completed the first MRI assessment.

MRI Procedures

We scanned infants in natural postprandial sleep, without sedation, in accordance with a protocol established by our research group (16). Imaging data were acquired on a 1.5-T magnet (MAGNETOM Avanto; Siemens Medical Systems, Erlangen, Germany) using the integral body coil. Infants were scanned in the supine position in the axial plane during free breathing. Full body imaging took ~20 min. We used a T1-weighted fast spin echo sequence with a repetition time of 514 ms, an echo time of 11 ms, an echo train length of 3, and three signal averages. Each slice was 5 mm thick with a 5-mm gap. The field of view was 300 $\times$ 300 mm with a matrix of 320 $\times$ 320 mm, leading to pixel sizes of 0.9375 $\times$ 0.9375 mm. AT volume was calculated for six regional depots. AT was classified as subcutaneous or internal; subcutaneous AT was further separated into superficial or deep, and the three compartments were divided into abdominal (image slices from the sacrum to the top of the liver) or nonabdominal depots. Individual compartments were summed to give total AT volume. We used the following ratio to assess AT distribution: internal abdominal AT/nonabdominal superficial subcutaneous AT. AT area (in square centimeters) for each slice was calculated as the sum of the pixels multiplied by the pixel area. AT volume (in cubic centimeters) for each slice was calculated by multiplying the area by the sum of the slice thickness (0.5 cm) and the interslice distance (0.5 cm). Images were

analyzed by a single observer using a commercially available software program (SliceOmatic, version 4.2; TomoVision, Montreal, Canada), widely used in body composition studies. This analysis was undertaken independently of the investigators by the VardisGroup (London, U.K. [www.vardisgroup.com]), and investigators were blinded to group status.

To measure IHCL, we acquired a three-plane half-Fourier acquisition single-shot turbo spin-echo (HASTE) localizer of the liver. This ensured accurate positioning of the voxel in the right lobe of the liver, avoiding blood vessels and other tissues. We obtained ^{1}H magnetic resonance spectra using point-resolved spectroscopy with the following parameters: repetition time 1,500 ms, echo time 135 ms without water suppression and with 128 signal averages, and a 15 × 15 × 15 mm voxel size. Spectra were analyzed using the advanced method for accurate, robust, and efficient spectral fitting (AMARES) algorithm in the MRUI software package, version 5 (17). Peak areas for water and lipid resonances were obtained, and T1 and T2 corrections were performed (18). Hepatic water was used as an internal standard, with results expressed as a CH_2 lipid/water ratio × 100. Spectra were analyzed by a single research radiographer blinded to the diabetes group.

Statistics

Data were analyzed using SPSS version 22 (IBM, Armonk, NY). Descriptive data are presented as the mean (SD) for normally distributed data, or the median and interquartile range where data were non-normal. Where data were normally distributed, independent-sample *t* tests were used for between-group comparisons. For other continuous data, *t* tests were applied to log-transformed data where this was normal; otherwise, the Mann-Whitney *U* test was applied to the original data. χ^2 tests were used to test for differences among categorical data. We compared the following in GDM group infants and control infants: total and compartmental AT volumes, AT distribution, and IHCL at each assessment and the change in total AT volume between assessments. We used statistically optimal indices to adjust AT volume for infant size. These are AT volume/length (cubed) in the neonatal period (first assessment) and AT volume/length (squared) in early infancy (second assessment) (19). IHCL in infants is correlated with postnatal age, but not with infant size (20), and was adjusted for the former. After adjustment for size, the results are not expressed in conventional units, and for ease of interpretation, we presented the mean percentage differences by comparing log-transformed outcomes between groups and exponentiating the regression coefficient. Using multivariable regression analysis (generalized linear models), we also adjusted outcomes for infant sex and maternal prepregnancy BMI. To check for the violation of regression assumptions, we assessed standardized residuals for normality. To further assess any possible influence of maternal prepregnancy BMI on the association between maternal GDM and infant adiposity, we performed a subgroup analysis in women with normal prepregnancy BMI (<25 kg/m^2). In order to assess whether differences in ethnicity influenced results, we also performed a sensitivity analysis using data only from Caucasian infants.

RESULTS

We approached the families of 425 infants in total. Recruitment is detailed in Fig. 1. Eighty-eight infants attended the first assessment; two infants did not settle sufficiently for image acquisition. Families were allowed time to consider the study, and, because it was difficult to predict uptake, two additional infants participated in the control group (i.e., 42 GDM group infants, 44 control infants). Seventy-six infants attended the second assessment. Ten infants did not attend because of illness (*n* = 4), because of travel (*n* = 3), or because the family no longer wished to participate (*n* = 3). The second scan was unsuccessful in three infants. Therefore, complete MRI data at the first and second assessments were obtained for 86 and 73 infants, respectively. Spectroscopy was performed at the end of the magnetic resonance sequence and was not obtained in a number of babies who woke or became restless. Spectra were available in 79 infants at assessment 1 and in 51 infants at assessment 2.

Mothers with GDM had greater prepregnancy BMI than mothers with normal glucose tolerance (Table 1). The majority of women with GDM received medical treatment (55%), as follows: metformin (36%), insulin (5%), or a combination of both (14%). HbA_{1c} was available in 33 of 42 women with GDM. The group had evidence of good glycemic control with a mean (SD) third-trimester

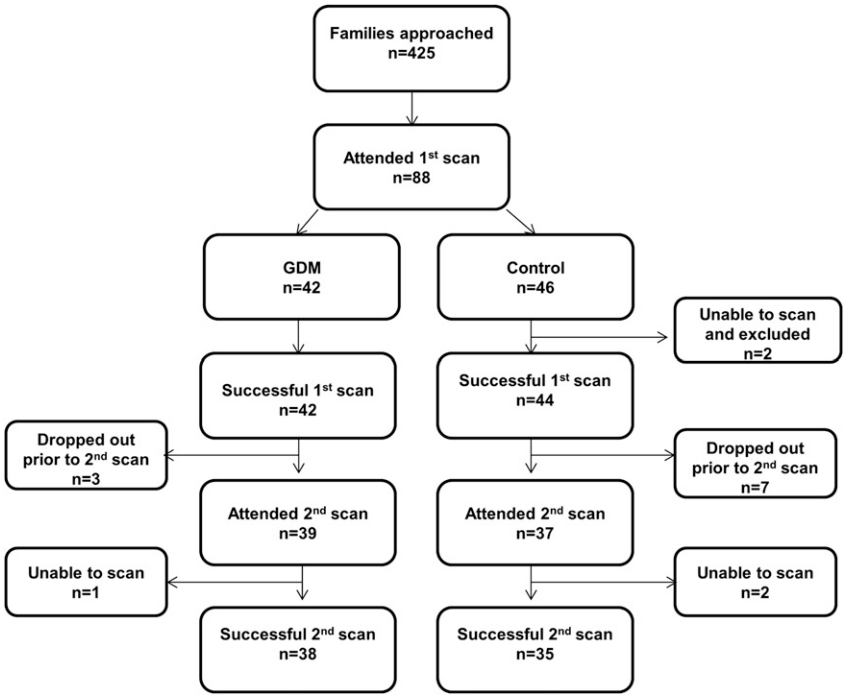

Figure 1—Flowchart detailing infant recruitment and magnetic resonance investigations.

Table 1—Maternal and infant characteristics comparing GDM and control groups

	GDM group (n = 42)	Control group (n = 44)	P value
Maternal characteristics			
Maternal prepregnancy BMI (kg/m^2)*	24.2 (21.7, 30.3)	21.9 (20.3, 24.5)	0.001
Caucasian (%)†	67	86	0.09
Maternal graduate (%)†	76	77	0.91
Infant characteristics at birth			
Gestation (weeks^{+days})	38^{+5} (1^{+1})	39^{+6} (1^{+1})	<0.001
Male sex (%)†	41	61	0.05
Weight (g)	3,440 (356)	3,632 (419)	0.02
Weight SDS	−0.06 (0.77)	0.28 (0.88)	0.06
Infant anthropometrics at assessment 1			
Age (days)*	11.0 (7.8, 14.3)	8.5 (2.0, 14.8)	0.22
Weight (g)	3,538 (385)	3,703 (471)	0.08
Weight SDS	−0.49 (0.76)	−0.12 (0.84)	0.04
Length (cm)	52.1 (1.7)	53.6 (2.4)	0.001
Length SDS	0.23 (0.88)	1.03 (1.24)	0.001
OFC (cm)	35.2 (1.2)	35.8 (1.4)	0.04
OFC SDS	−0.37 (0.85)	0.11 (1.01)	0.02
Total AT volume (cm^3)	961 (189)	989 (241)	0.55
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio	0.06 (0.02)	0.06 (0.02)	0.73
IHCL (CH_2/H_2O ratio)*	1.01 (0.55, 1.95)	0.88 (0.35, 1.75)	0.44
Infant anthropometrics at assessment 2	(n = 38)	(n = 35)	
Age (days)*	70.5 (67, 74)	71 (66, 74)	0.75
Weight (g)	5,755 (625)	5,695 (619)	0.68
Weight SDS	0.46 (0.93)	0.22 (0.81)	0.24
Weight gain SDS	0.62 (1.08)	0.05 (0.95)	0.02
Length (cm)	59.5 (2.1)	60.3 (1.7)	0.09
Length SDS	0.62 (0.95)	0.85 (0.91)	0.29
OFC (cm)	39.5 (1.2)	40.0 (1.1)	0.05
OFC SDS	−0.11 (0.98)	0.14 (0.78)	0.22
Total AT (cm^3)	2,185 (416)	1,938 (403)	0.01
Change in total AT (cm^3)	1,232 (402)	968 (425)	0.01
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio	0.06 (0.02)	0.06 (0.02)	0.75
IHCL (CH_2/H_2O ratio)‡	1.92 (0.29)	1.85 (0.36)	0.85
Feeds†			
Exc/pred breast-fed	71	74	0.37
Mixed fed	5	9	
Exc/pred formula fed	24	17	

Data are reported as the mean (SD), unless otherwise indicated. P values were obtained by independent-sample t test (GDM vs. control) except where noted. *Values are given as the median (interquartile range), with P value obtained by Mann-Whitney U test. †Values are given as %, with P value obtained by χ^2 test. ‡Values are given as the geometric mean (SD), with P value obtained by independent-sample t test after log transformation. Exc, exclusively; pred, predominantly.

HbA_{1c} level of 5.3% (0.3) (34.9 mmol/mol [3.4]). GDM group infants were born earlier than the control infants and had a lower birth weight, but there was no statistical difference in birth weight SD score (SDS) between groups (Table 1). The SDS for weight, length, and OFC was significantly lower in GDM group infants at the first assessment, but was similar to that of control infants at the second assessment. Weight gain SDS between birth and assessment 2 was greater in the GDM group. The proportions receiving exclusive or predominant breast-feeding by the second assessment were similar in the GDM and control groups (Table 1).

At assessment 1, there were no significant differences between GDM and control infants in unadjusted total AT volume, AT distribution, or IHCL level (Table 1). There were no differences in compartmental AT volumes (Supplementary Table 1). At assessment 2, total AT volume was greater in GDM group infants than in control infants (mean difference 247 cm^3 [95% CI 56, 439], P = 0.01.) There were no significant differences in AT distribution or in IHCL level between groups (Table 1). Greater AT volumes were seen in GDM group infants compared with control infants in all compartments, though the differences did not reach statistical significance for abdominal deep subcutaneous or internal abdominal compartments (Supplementary Table 1).

After adjustment for infant size (19), there was no significant difference in total AT volume between GDM and control group infants at assessment 1 (Table 2). Although several AT compartments appeared greater in the GDM group, there were no statistically significant differences between groups for any of the AT compartments (Supplementary Table 2). At assessment 2, total AT volume was greater in GDM group infants (mean difference 16.0% [95% CI 6.0, 27.1], P = 0.002), and the change in total AT volume between assessments was

Table 2—Adjusted percentage differences in total AT, AT distribution, and IHCL level for infants of mothers with GDM compared with control infants

	Model 1			Model 2		
Outcomes	Difference (%)	95% CI	*P* value	Difference (%)	95% CI	*P* value
Assessment 1						
Total AT	6.9	−1.4, 15.9	0.11	5.4	−3.6, 15.6	0.24
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio				1.2	−11.3, 15.6	0.86
IHCL*						
Assessment 2						
Total AT	16.0	6.0, 27.1	0.002	12.5	1.0, 25.0	0.03
Change in total AT	35.8	11.7, 65.2	0.003	32.4	5.2, 66.3	0.02
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio				−0.2	−15.1, 17.2	0.98
IHCL	5.7	−30.2, 59.6	0.79	3.5	−35.4, 65.6	0.89

Model 1, adjustment of AT for body size using indices (18) (not applicable for AT ratios) and IHCL for postnatal age; model 2, same as model 1 plus adjustment for infant sex and maternal prepregnancy BMI. *Non-normal distribution, and therefore the percentage difference, was not calculable.

greater in GDM group infants compared with control infants (mean difference): 35.8% [95% CI 11.7, 65.2], $P = 0.003$) (Table 2). All AT compartments were greater in GDM group infants, although the difference in the abdominal deep subcutaneous compartment was not statistically significant (Supplementary Table 2).

There was no interaction detected between maternal GDM status and infant sex for any outcome at either assessment. After adjustment for infant sex and maternal prepregnancy BMI, the results of comparisons between GDM and control groups at the first and second assessments were relatively unchanged (Table 2 and Supplementary Table 2). Sensitivity analyses in women with normal prepregnancy BMI and in Caucasian infants did not significantly alter the results; the total AT volume at assessment 2 remained statistically greater in GDM group infants after adjustment for potential confounders.

CONCLUSIONS

We show that adiposity in infants of mothers with GDM appears to be amplified in early infancy. GDM group infants had on average 16% greater total AT volume compared with control infants by 2 months of age, despite no significant difference soon after birth. To the best of our knowledge, this is a novel observation. The increase in adiposity was not accompanied by altered AT distribution or IHCL content. These conclusions remain robust to adjustment for maternal prepregnancy BMI, supporting an independent effect of GDM on infant adiposity.

The strengths of our study included the use of a direct method to accurately quantify total and compartmental AT volume, with adequate power to detect differences likely to be clinically relevant in a relatively small number of infants. A further strength was the longitudinal design, enabling assessment of the evolution of adiposity in early infancy. Differences in total and compartmental AT volumes at 8–12 weeks of age were consistent after adjustment for confounders and in sensitivity analyses, leading to increased confidence in the findings.

A limitation of our study was that we did not examine for the effect of preexisting diabetes on offspring adiposity. However, the metabolic effects of exposure to diabetes in utero appear to be similar regardless of diabetes type (21). Our study was also not designed to enable the exploration of intrauterine and genetic influences, but sibling comparison studies (3,4) strongly support an intrauterine effect that is independent of genetic predisposition.

The finding of similar total AT volume in infants with GDM and control infants in the early newborn period contrasts with the greater adiposity in infants of mothers with diabetes identified in some previous studies (7,22,23), but is in keeping with results from two other recent studies (24,25). It is possible that strict maternal glucose control in our cohort may have attenuated any between-group neonatal differences. An Australian study (24), using air displacement plethysmography, reported similar body fat percentages in the infants of mothers with and without GDM. The authors attributed this to good maternal glucose control, with a mean third-trimester HbA_{1c} level for the group of 5.4%, which is similar to that in our study. In contrast with our study, longitudinal data were not obtained. Brumbaugh et al. (25) also used air displacement plethysmography to measure body fat percentage, with similar findings. In addition, the authors (25) measured two AT compartments using MRI (defined as intra-abdominal or subcutaneous fat), and reported similar volumes in infants of mothers with GDM and control infants, but acknowledged a limited power to detect differences. Our results corroborate these findings of similar AT distribution in an adequately powered cohort. Intriguingly, and in contrast with our own study, Brumbaugh et al. (25) found IHCL levels to be greater in infants of mothers with GDM. However, they estimated IHCL levels without adjustment for intrahepatic water and studied only 20 infants. The treatment of maternal GDM and glycemic control were not described, and exploration of the relative influences of maternal GDM and obesity was not possible because all mothers with GDM were obese (prepregnancy BMI >30 kg/m^2) (25). The differences they report in IHCL levels may relate to maternal obesity, because maternal BMI is positively correlated with IHCL level in infants (20).

The International Association of Diabetes and Pregnancy Study Groups proposed new criteria for universal screening for maternal GDM in 2010 (26). In a large Spanish study, these criteria resulted in significantly improved

pregnancy outcomes, including a reduced risk of large-for-gestational-age infants (27). Two randomized controlled trials demonstrated reduced birth weight (28) and neonatal fat mass (29) with treatment of mild GDM. Although differences may exist in our study population and the criteria used to diagnose GDM, our findings support the concept that more stringent screening and treatment strategies for GDM may attenuate the differences in adiposity between infants of mothers with GDM and those without GDM at birth. Of note, there is evidence that benefits may not persist beyond the newborn period, as follow-up studies (30,31) have not shown a reduction in early childhood obesity with treatment. The later development of obesity in childhood might be considered to be due to exposure to an obesogenic environment rather than to a direct effect of maternal diabetes; however, our study suggests that this is unlikely to be the case because differences in adiposity between GDM and control infants emerge early in infancy during the period of breast-feeding.

We identified a striking difference in total AT volume in GDM group infants compared with control infants by 10 weeks. This was particularly notable because greater adiposity was not accompanied by discernible differences in body weight or length, although GDM group infants demonstrated rapid weight gain, which is itself a risk for greater adiposity in childhood (32). This appeared to occur as a result of greater AT deposition. Our study was not powered to detect small differences in regional AT compartments, and it is possible that GDM infants had subtle differences in AT from birth, which may have evolved in early infancy. What is remarkable is the extent to which total AT differed by the second assessment. The mechanisms that lead to increased adiposity in infants of mothers with GDM in early infancy merit consideration. One possible explanation is that intrauterine or neonatal exposure to an excess of nutrients may alter hypothalamic sensing, leading to alterations in satiety and appetite (33,34). Another potential mechanism for the differences described concerns differences in breast milk composition. The proportion of breast-fed infants in our study was similar in both groups. It has been suggested (35) that neonatal ingestion of breast milk from mothers with diabetes may increase the risk of overweight in early childhood. Breast milk alterations, including higher glucose concentration, have been demonstrated in mothers with type 1 diabetes, which may influence infant body composition (36,37). The exploration of breast milk composition in mothers with GDM has been limited, and an examination of the relationship among GDM status, breast milk composition, and infant adiposity may provide further insight.

The relative contributions of maternal BMI and diabetes on offspring adiposity remain uncertain (4,5). The HAPO group found that both maternal GDM (diagnosed post hoc using International Association of Diabetes and Pregnancy Study Groups criteria) and, to a lesser extent, maternal obesity are independently associated with newborn adiposity, and that their combination has a greater impact than either alone (38). We found that differences in adiposity between GDM and control groups at 10 weeks were slightly attenuated after adjustment for maternal prepregnancy BMI. Our findings support an independent effect of maternal GDM on infant adiposity, with a lesser contribution from maternal prepregnancy BMI.

In conclusion, in this contemporary predominantly breast-fed cohort with good glycemic control in pregnancy, we demonstrate that infants of mothers with GDM have significantly greater total AT volume at 2–3 months of age compared with control infants. This is particularly striking given that there was no significant difference in total adiposity at birth. This indicates, first, that careful control of GDM may not be sufficient to ameliorate the effects of maternal GDM on later infant health and, second, that this may be mediated by excess adiposity. Because adiposity appears to track from infancy into childhood (39), this is a plausible harbinger of longer-term risks to health. We suggest that a key research priority is to examine the evolution of early infancy adiposity into childhood and the potential effects on metabolic health in the offspring of mothers with GDM. Reduction in postnatal adiposity may be a therapeutic target to break the cycle of increasing population obesity and related complications, including type 2 diabetes.

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