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CLINICAL RESEARCH ARTICLE

Maternal obesity and gestational diabetes mellitus affect body composition through infancy: the PONCH study

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BACKGROUND: To determine how maternal obesity or gestational diabetes mellitus (GDM) affect infant body size and body composition during the first year of life.
METHODS: Eighty three normal-weight (NW) women, 26 obese (OB) women, and 26 women with GDM were recruited during pregnancy. Infant body composition was determined by air-displacement plethysmography at 1 and 12 weeks, and anthropometric measurements made until 1 year of age.
RESULTS: Girl infants born to OB women and women with GDM had a higher body-fat percentage (BF%) at 1 and 12 weeks of age than girls born to NW women. Girls had higher BF% than boys in OB and GDM groups only. Maternal HbA1c and fasting plasma glucose correlated with girl infant BF% at 1 week of age. Maternal weight at start of pregnancy correlated with birthweight in NW and OB groups, but not the GDM group. OB group infants showed greater BMI increases from 1 week to 1 year than both NW and GDM group infants.
CONCLUSION: Results show that both maternal glycaemia and obesity are determinants of increased early life adiposity, especially in girls, with glycaemic levels being more influential than maternal weight for infants born to women with GDM.

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INTRODUCTION

Obesity has become an epidemic, making it important to establish when obesity starts in life and what influences its subsequent development. An increasing amount of literature suggests that adiposity and risk of metabolic syndrome are already programed in utero and during infancy; the "first 1000 days" from conception to 2 years of age being considered of particular importance.[1–3] This highlights the need to study timing of adiposity and identify risk factors that may enable preventative intervention early in life.

It is well established that fast weight gain in infancy is linked to later childhood obesity,[1,4,5] although less is known regarding the importance of changes in body composition. Body composition goes through large changes during infancy, with fat percentage as measured by air-displacement plethysmography (ADP), increasing from ~13 to 26% between weeks 1 and 12 of life,[6] indicating that a large proportion of early weight gain is due to fat mass. Changes during the first 3 months of life are of particular interest because rapid weight gain in this period is associated with overweight and high adiposity in childhood,[7] and is linked to metabolic risk in early adulthood.[8]

A large body of evidence has identified high maternal BMI as a risk factor for increased birthweight.[9,10] High birthweight, independent of gestational age (GA), is a risk factor for later obesity.[11,12] Using ADP, some studies have linked a high maternal BMI to a high fat mass or high fat percentage in offspring at birth,[13] or at 20 days,[14] while others have not seen a relationship.[6,15]

Gestational diabetes mellitus (GDM) has also been identified as a risk factor for high infant adiposity as measured at birth by skinfold thickness,[16] dual-energy X-ray absorptiometry (DXA)[17] or ADP.[18] Children born to mothers with diabetes during pregnancy have a higher risk of developing metabolic disease later in life, which might partly originate from the intrauterine milieu and already having an unfavourable body composition in infanthood.[19] Two studies have shown that dysregulated glucose homoeostasis in those with GDM and high BMI are independently associated with increased newborn weight and adiposity at birth, as measured by skinfold thickness or DXA.[16,17] Another large study measuring body composition by ADP in infants of women with well-regulated GDM, however, showed no increase in adiposity in infants at birth.[20]

Interestingly, there may be a sex difference in how maternal BMI and/or dysregulated glucose levels affect infant body composition. Lingwood et al. showed that, in GDM pregnancies, maternal fasting blood glucose levels determined adiposity in newborn male offspring, and maternal pre-pregnancy BMI determined adiposity in female offspring.[18] Henriksson et al., on the other hand, showed that high maternal fat mass and maternal insulin resistance were only associated with fat mass in 1-week-old infant girls.[21]

With conflicting results regarding the impact of maternal obesity and diabetes on body composition in early infancy, and a scarcity of studies focusing on how maternal obesity or dysregulated glucose metabolism during pregnancy affect adiposity development from birth through infanthood, there is a need for more longitudinal studies using reference methods such as ADP.

PONCH—Pregnancy Obesity Nutrition Child Health—is a longitudinal study of normal-weight, obese, and GDM-diagnosed pregnant women and their children.[22–24] The study includes

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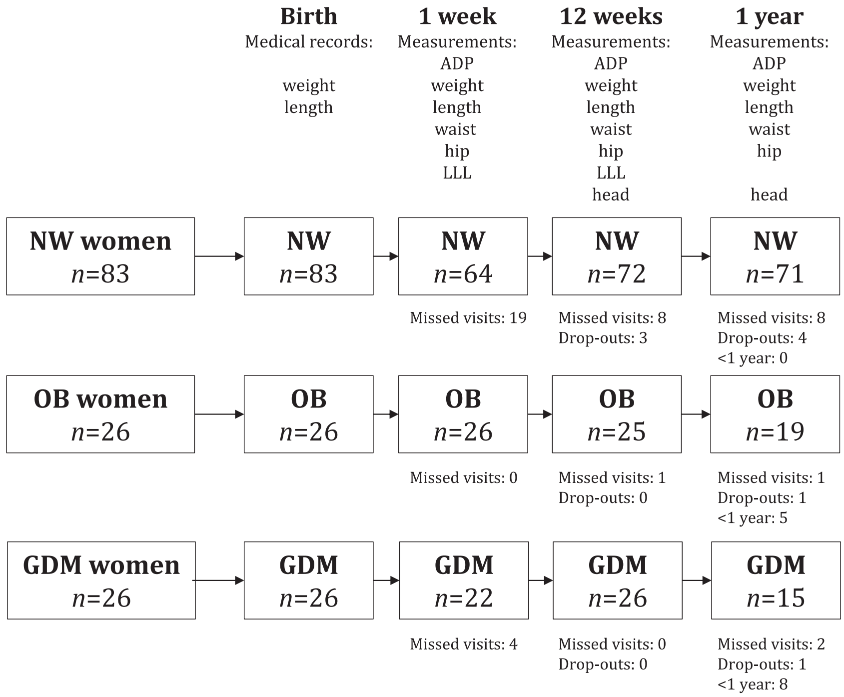

Fig. 1 Study design. Three groups of women and their infants were recruited; NW normal weight pregnant women, OB obese pregnant women (BMI > 30), and GDM pregnant women with gestational diabetes mellitus. Where children have not yet reached the 1-year follow-up, this has been noted as <1 year. ADP air-displacement plethysmography body composition determination, LLL lower leg length

infant/child follow-ups from 1 week to 6 years of age. The present analysis is the first to be published on children in the PONCH study. The aim was to measure infant anthropometry during the first year of life, with a focus on body composition during the first 12 weeks, in order to determine how this was affected by maternal obesity and/or glycaemic status. We hypothesize that maternal glucose metabolism, in particular, is a predictor of infant body composition.

METHODS

Ethical approval

The study was approved by the ethics committee at the University of Gothenburg (Dnr 402-08). All women received oral and written information about the study and gave informed written consent before enrolment of themselves and their children.

Study design

Subjects. Normal weight (NW: BMI 18.5–24.9 kg/m^2) and obese (OB: BMI ≥ 30 kg/m^2) pregnant women were recruited from six antenatal health units within the Gothenburg area as part of the PONCH study, as previously described.[22,24] In addition, the PONCH study included women with GDM, irrespective of BMI, recruited at the Sahlgrenska University Hospital at time of diagnosis.[23] In Gothenburg at the time of the present study (2009–2018), all pregnant women had non-fasting blood glucose measured regularly throughout pregnancy, and women with an elevated non-fasting glucose (>8 mmol/l) underwent OGTT. GDM diagnosis was then based on the European Association for the Study of Diabetes 1991 criteria.[25] GDM was diagnosed if any of the following values was observed: fasting plasma glucose ≥7.0 mmol/l, oral glucose tolerance test 2-hour plasma glucose ≥10.0 mmol/l, and random non-fasting plasma glucose ≥12.2 mmol/l. GDM-women included in the present study were diagnosed at 27 ± 7 gestational weeks, with 21% diagnosed on fasting glucose-values (diagnostic value 7.3 ± 0.4 mmol/l) and 79% on 2 h OGTT values (diagnostic value 10.9 ± 1.1 mmol/l), four (out of 26) women received insulin treatment during pregnancy and 36% reported a family history of diabetes.

Women enroled in PONCH attended study visits at the Sahlgrenska University Hospital each trimester (weeks 8–12 (trimester one), 24–26 (two), and 35–37 (three)) during pregnancy.[22] The GDM group attended their first visit after diagnosis, usually during trimester three. At the third trimester visit, all women were asked whether they wanted their child to be included in the study after birth.

Children included in the study were divided into groups corresponding to the category assigned to their mother (NW, OB, or GDM; Fig. 1). The study is ongoing with the current manuscript based on data from children included April 2009–May 2018.

Maternal visits

Maternal pregnancy visits have been described previously.[22] These were all in the morning after an overnight fast, and included anthropometric measurements, blood sampling and completion of lifestyle questionnaires. HbA1c and glucose levels were analyzed at the accredited (SWEDAC ISO-15189; No.1240) Clinical Chemistry Laboratory, Sahlgrenska University Hospital. Educational level was based on the women's highest attained level and classified as elementary school, 2 years of high school, 3 years of high school, <3 years of university, or ≥3 years of university.

NW- and OB-women were randomized into diet-intervention or control groups.[22] In the current study, equal numbers of children from mothers in intervention and control groups were included, and were evenly distributed in the NW and OB groups. No differences between maternal intervention and control groups were found for any of the outcome measures presented in this paper, so only combined data for the intervention/control groups have been used. GDM-women received standard obstetric hospital care including diet and lifestyle advice. As GDM-women did not attend study visits early in pregnancy, trimester one weight was collected from medical records.

Infant anthropometric measurements

At birth. Birthweight and length were collected from medical records, and BMI and weight/length calculated. Standard deviation scores (SDS) were calculated for all growth data and compared with data from healthy infants born in Sweden from 1990 to 1999.[26–28]

During infancy. Anthropometric and body composition measurements were made at visits at 1 week (4–10 days) and 12 weeks (80–90 days) after birth, and anthropometric measurements at 1 year (355–375 days). There were no differences between groups in age at visits. Due to the short age intervals accepted within the protocol, some visits were missed (Fig. 1). Measurements were not made if infants were unwell; contributing to some missed visits at 12 weeks and 1 year. At 1 week, the most common reason for missed visit was that the mother had not recovered after delivery. Reason for study drop-out was generally lack of time.

During the two first visits, weight, body-fat percentage (BF%), fat mass (FM), and fat-free mass (FFM) were measured by air-displacement plethysmography (ADP) using the PEAPOD (software version 3.3.0; COSMED, Italy).

Length and hip and waist circumference were measured at all visits, with the addition of lower leg length (LLL) at the first two visits and head circumference at the last two. All measurements were made to the nearest 0.5 cm with the infant lying down. Length was measured using a length board; waist circumference was measured immediately above the navel; and hip circumference at the widest part of the hip. LLL was measured with the knee bent at a 90° angle using a sliding caliper from the heel to the top of the knee. At each visit, mothers were asked whether they were fully, partly, or not breastfeeding.

Growth measure calculations

The present Swedish growth references were used to convert measures of length, weight, and head circumference obtained between 1 week and 1 year,[26] and the calculated BMI,[28] into age- and sex-specific SDS-values.

Statistical methods

All statistical methods were specified prior to start of data processing and analysis. Continuous variables were described by mean and standard deviation, and categorical variables by number and percentage. For pairwise tests between two groups, Fisher's exact test was used for dichotomous variables, Mantel–Haenszel chi-squared test for ordered categorical variables and a *t*-test for continuous variables. To test differences within a group, Wilcoxon signed–rank test was used for continuous variables.

Longitudinal study of continuous growth data was performed by random coefficients models using available visits with GA-adjusted age at the 1 week, 12 week, and 1 year visits as time scale. For the outcome measures collected at all three visits, a piecewise linear polynomial function of age was applied. The fixed effects included the three study groups, age (either linear or piecewise linear), and interaction between the group and age. The random effects included intercept and age variable (s). The best covariance matrix was selected based on lowest Akaike's Information Criterion using an unstructured, autoregressive, and compound symmetry covariance pattern for all data together and separately per group. Unadjusted analyses and analyses adjusted for GA and sex were performed. When group effects were to be tested between the sexes, the following interactions were added to the fixed effects: sex–group, sex–age, and sex–GA. From the random coefficients models, least square means with 95% CIs were presented. The assumption of normality was checked and found to be satisfied. Pearson and partial correlations were estimated when relationships between mother and child data were studied. Correlation statistics were adjusted for GA and sex, where appropriate.

All tests were two-tailed and conducted at a 0.05 significance level. All analyses were performed using SAS Software version 9.4 (SAS Institute Inc., Cary, NC) and IBM SPSS version 23.0 (IBM SPSS Statistics, Armonk, NY).

RESULTS

Maternal characteristics

Maternal and birth characteristics are displayed in Table 1. In total, 83 infants born to NW women (NW; 41 girls, 42 boys), 26 born to OB women (OB; 9 girls, 17 boys), and 26 born to women with GDM (GDM; 16 girls, 10 boys) were included.

Maternal BMI differed significantly between all three groups, with the highest BMI in OB women and the lowest in NW women (Table 1). NW women gained more weight than OB women. Infants of women with GDM were born at an earlier GA compared with infants born to NW mothers.

Fasting glucose was higher in both OB and GDM compared with NW women, with no significant difference between OB and GDM-women (though glucose levels for all NW and OB women were below <6.1 mmol/l, the defined threshold for impaired fasting glucose[25]). HbA1c, however, differed significantly between all three groups.

NW women breastfed to a greater degree than OB women (at 12 weeks; $P = 0.011$) and GDM-women (at 1 and 12 weeks; $P = 0.0043$ and $P = 0.012$, respectively). NW women had a higher level of education than OB. There were no differences between groups in self-reported energy intake or physical activity during pregnancy (data not shown) and none of the women in the study used tobacco or alcohol (alcohol intake of <1 g/day was defined as no intake).

OB and GDM group infants were heavier than NW group infants at birth

Birth characteristics are presented in Table 1. There was no significant difference in sex distribution between groups. After adjusting for sex and GA, infants born to both OB and GDM-women were heavier compared with infants born to NW women. GDM group infants were also born longer than NW group infants. Compared to the average Swedish population, NW group infants were shorter ($length_{SDS}$) but had higher $weight/length_{SDS}$ and BMI_{SDS}, while OB group infants were of similar length to the average population but had higher $weight/length_{SDS}$ and BMI_{SDS}. GDM group infants were also of similar length to the average population but were heavier ($weight_{SDS}$) and had higher BMI_{SDS}.

BF% and FM was higher in girls born to women with obesity or GDM than to NW women

Infant body composition data at 1 and 12 weeks are shown in Fig. 2 and Supplemental Table S1. BF% and FM were higher in GDM group infants compared to NW group infants both at 1 week ($P = 0.004$ and $P = 0.003$, respectively) and 12 weeks ($P = 0.008$ and $P = 0.027$, respectively). When grouped by sex, there were no differences between groups in body composition for boys. In contrast, for girls, BF% and FM were higher in OB and GDM groups compared to NW at both 1 week (OB, $P = 0.017$ and $P = 0.005$, respectively; GDM, $P = 0.0002$ and $P = 0.0006$, respectively) and 12 weeks (OB, $P = 0.029$ and $P = 0.043$, respectively; GDM, $P = 0.010$ and $P = 0.037$, respectively) (Fig. 2). There were also differences between girls and boys within the OB and GDM groups, with higher BF% in girls than boys at 1 and 12 weeks in the OB group (both $P < 0.01$) and at 1 week in the GDM group ($P < 0.05$); this was not seen in the NW group. There were no significant differences in FFM.

Table 1. Maternal characteristics, education and breastfeeding and infant birth characteristics

	NW			OB			GDM			*P* (between groups)		
	n	Mean (SD)	*P* (SDS)[a]	*n*	Mean (SD)	*P* (SDS)[a]	*n*	Mean (SD)	*P* (SDS)[a]	NW vs. OB	NW vs. GDM	OB vs. GDM
Maternal data												
Age (y), T1	83	31.3 (3.8)		26	31.0 (3.8)		26	32.6 (4.5)		0.72[d]	0.13[d]	0.16[d]
BMI, T1 (kg/m^2)	83	22.3 (1.5)		26	34.9 (3.3)		26	27.1 (6.6)		**<0.0001**[d]	**0.001**[d]	**<0.0001**[d]
Gestational weight gain (kg)	81	12.7 (3.6)		25	9.6 (5.8)		26	10.7 (5.7)		**0.02**[d]	0.12[d]	0.48[d]
Gestational age (w)	83	40.2 (1.1)		26	40.1 (1.8)		26	39.4 (1.3)		0.71[d]	**0.004**[d]	0.16[d]
Fasting Glucose (mmol/l), T3	81	4.48 (0.40)		25	4.75 (0.34)		25	5.10 (0.90)		**0.003**[d]	**0.003**[d]	0.08[d]
HbA1c (mmol/mol), T3	81	29.5 (2.9)		25	31.1 (2.3)		25	34.7 (4.2)		**0.01**[d]	**<0.0001**[d]	**0.0006**[d]
Education level												
2 years of high school *n* (%)		0 (0.0%)			0 (0.0%)			2 (8.7%)				
3 years of high school *n* (%)		9 (11.1%)			10 (40.0%)			4 (17.4%)				
<3 years of university *n* (%)		14 (17.3%)			6 (24.0%)			3 (13.0%)				
≥3 years of university *n* (%)		58 (71.6%)			9 (36.0%)			14 (60.9%)		**0.0003**[b]	0.065[b]	0.28[b]
Breastfeeding fully/partly/not												
At 1 week (%)	82	(93/6/1)		26	(77/23/0)		26	(69/27/4)		0.07[c]	**0.004**[c]	0.40[c]
At 12 weeks (%)	80	(81/15/4)		25	(56/32/12)		23	(57/30/13)		**0.01**[c]	**0.01**[c]	0.98[c]
At 1 year (%)	77	(0/21/79)		21	(0/19/81)		17	(0/12/88)		1.00[c]	0.63[c]	0.88[c]
Birth data												
Sex—boys n (%)		42 (50.6%)			17 (65.4%)			10 (38.5%)		0.27[b]	0.39[b]	0.10[b]
Birthweight (kg)	83	3.64 (0.47)		26	3.84 (0.58)		26	3.76 (0.55)		**0.04**[f]	**0.02**[f]	0.79[f]
Birthweight SDS	83	−0.15 (0.97)	0.30[e]	26	0.32 (1.06)	0.14[e]	26	0.52 (1.10)	**0.025**[e]	**0.04**[f]	**0.02**[f]	0.76[f]
Birth length (cm)	82	50.5 (2.1)		25	51.4 (2.4)		26	50.9 (2.0)		0.07[f]	**0.01**[f]	0.30[f]
Birth length SDS	82	−0.54 (1.20)	**0.0001**[e]	25	−0.01 (1.08)	0.98[e]	26	0.17 (0.98)	0.23[e]	0.07[f]	**0.01**[f]	0.36[f]
Weight/length (kg/m)	82	7.18 (0.73)		25	7.44 (0.90)		26	7.37 (0.90)		0.08[f]	**0.04**[f]	0.83[f]
Weight/length SDS	82	0.34 (1.00)	**0.002**[e]	25	0.43 (0.92)	**0.029**[e]	26	0.57 (1.27)	0.06[e]	0.54[f]	0.78[f]	0.72[f]
BMI (kg/m^2)	82	14.2 (1.2)		25	14.4 (1.4)		26	14.5 (1.6)		**0.29**[f]	0.20[f]	0.91[f]
BMI SDS	82	1.64 (1.06)	**<0.0001**[e]	25	1.65 (0.99)	**<.0001**[e]	26	2.21 (1.46)	**<.0001**[e]	0.49[f]	0.23[f]	0.63[f]
LGA (%)	82	0		25	4		26	19		0.47[b]	**0.001**[b]	0.21[b]

Significant *p*-values are displayed in bold

BMI body mass index, *GDM* gestational diabetes mellitus, *LGA* large for gestational age based on either length or weight, *NW* normal weight, *OB* obese, *SDS* standard deviation score, *T1* trimester one, *T3* trimester three

[a]Compared with the average Swedish population[28–30]

[b]For pairwise comparison between groups, Fisher's exact test (2-sided) was used for dichotomous variables. For pairwise comparisons between groups with respect to LGA variables, Fisher's Exact test (2-sided) was used, not adjusted due to low number of cases with LGA

[c]For pairwise comparison between groups, the Mantel–Haenszel chi square test for ordered categorical variables

[d]For pairwise comparison between groups, a *t*-test for continuous variables

[e]For comparison within groups, the Wilcoxon signed–rank test was used

[f]*P*-values for birth data were adjusted for sex and gestational age and analyses were performed using an ANCOVA for continuous variables

All sex-specific differences remained significant after adjustment for breastfeeding for both OB and GDM compared to NW. However, for boys and girls combined, the difference in FM between NW and GDM groups at 12 weeks was no longer significant ($P = 0.076$). All sex-specific differences between NW and GDM also remained significant when adjusting for education. For boys and girls combined, differences in FM and BF% between NW and GDM lost significance at 12 weeks ($P = 0.057$ and $P = 0.054$, respectively). For OB vs. NW, three significances were lost when adjusting for education; FM in girls at 12 weeks ($P = 0.10$), BF% at 1 week ($P = 0.082$), and BF% at 12 weeks ($P = 0.13$).

Maternal glycemic status and weight correlated with body composition in girls

For the whole population, corrected for GA and sex, maternal glucose and HbA1c levels in trimester three correlated with BF% and FM in 1 week old infants (Fig. 3a–d). When grouped by sex, there were strong correlations between maternal glucose metabolism and infant BF for girls, but not for boys. These correlations were not apparent within the NW, OB, and GDM groups, either overall or when grouped by sex, except for the GDM group, where there was a strong correlation between maternal glucose level and infant BF% at 1 week in girls ($r = 0.79$ [$P = 0.002$], $n = 12$).

For the overall population, after adjustment for GA and sex, maternal weight in trimester one correlated with BF% and FM at 1 week (Fig. 3e–f). When grouped by sex, there were correlations between maternal weight in trimester one and infant BF% and FM in girls only. Correlations with weight were not as strong as with glucose and HbA1c.

There were no correlations between BF% or FM at 12 weeks with maternal weight, glucose, or HbA1c levels.

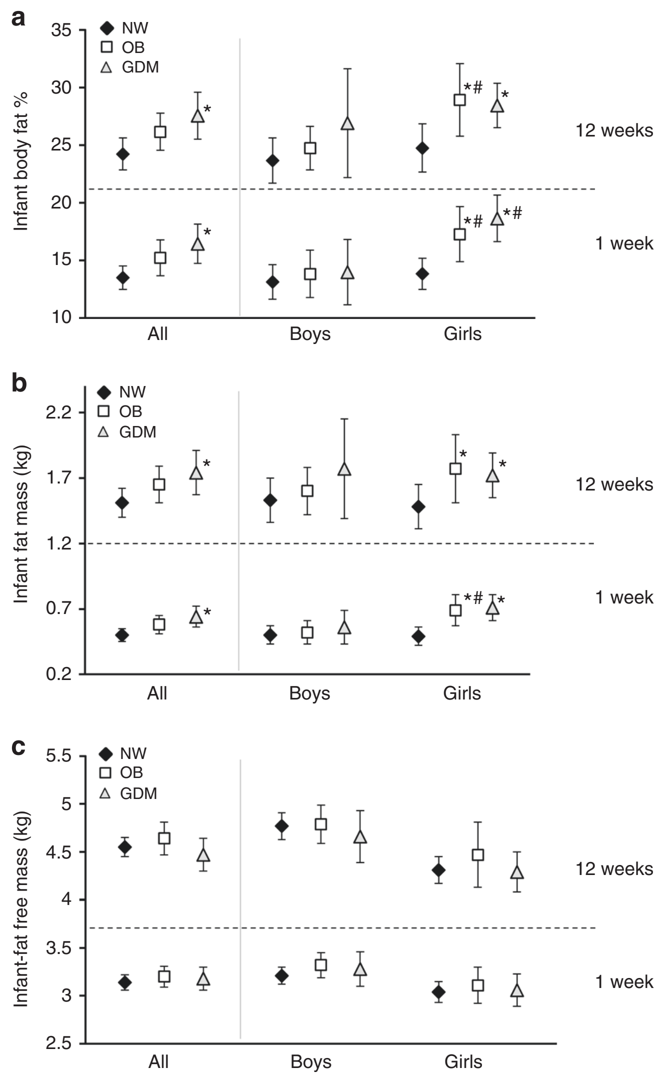

Fig. 2 Body composition at 1 and 12 weeks after birth in infants born to normal-weight (NW) women, obese (OB) women, and women with gestational diabetes mellitus (GDM). Points show mean ± CI as calculated by the random coefficient model. NW; $n = 83$ (42 boys, 41 girls), OB; $n = 26$ (17 boys, 9 girls); GDM; $n = 26$ (10 boys, 16 girls). *significant difference vs. NW. #significant difference boys vs. girls. For *P*-values see Supplemental Table S1

Infant anthropometry 1 week to 1 year

OB group infants had highest weight, BMI and hip circumference at 1 year. Anthropometry measurements are presented in Supplemental Tables S2–S4. Weight$_{SDS}$, length$_{SDS}$, BMI$_{SDS}$, weight/length$_{kg/m}$, and waist and hip circumference are visualized in Fig. 4. At week 1, weight$_{SDS}$ and BMI$_{SDS}$ were higher for GDM vs. NW group infants, and OB group infants were longer than NW group infants (length$_{cm}$ and length$_{SDS}$). No differences in weight, length, weight/length$_{kg/m}$, or BMI were found between groups at 12 weeks. At 1 year, OB group infants had higher weight$_{kg}$, weight/ length$_{kg/m}$, BMI$_{kgm2}$, and BMI$_{SDS}$ compared with both NW and GDM group infants.

Hip circumference was greater for OB than NW group children at 1 year. There were no significant differences in waist circumference, LLL or head circumference at any time point.

When controlled for breastfeeding, differences in weight$_{kg}$, weight/ length$_{kg/m}$, and BMI $_{kgm2}$ at 1 week became significant for NW vs. GDM group infants ($P = 0.039$, $P = 0.049$ and $P = 0.049$, respectively) All other significances remained.

Growth was more rapid in OB compared with NW and GDM group infants from 1 week to 1 year. The increase in weight/length from 1 week to 1 year was significantly greater in the OB group than both the NW and GDM groups ($P = 0.044$ and $P = 0.014$, respectively). Over the same time period, increases in weight$_{kg}$, BMI$_{kgm2}$, and BMI$_{SDS}$ were greater in the OB than GDM group ($P =$ 0.039, $P = 0.006$, and $P = 0.028$ for weight$_{kg}$, BMI$_{kgm2}$, and BMI$_{SDS}$, respectively), whereas the increase in hip circumference was greater in the OB than NW group ($P = 0.014$).

Sex differences: OB group girls were larger at 12 weeks and OB group boys at 1 year compared with NW and GDM group counterparts. When grouped by sex, growth differences were apparent between sexes (Supplemental Tables S1–S3). For girls, group differences were apparent at the earlier time points, with higher weight$_{kg}$, weight/length, BMI$_{kgm2}$, and BMI$_{SDS}$ at 12 weeks for OB girls compared with NW girls. In contrast, for boys, the OB group had higher weight/length and hip circumference than the NW group at 1 year.

Maternal weight correlated with infant weight for NW and OB groups only. Maternal weight at the start of pregnancy correlated with infant birthweight and infant weight at 1 week for the whole population adjusted for GA and sex ($r = 0.29$ [$P = 0.001$] and $r =$ 0.22 [$P = 0.02$], respectively). When grouped by maternal category, these correlations were observed in NW and OB groups (Fig. 5), but not the GDM group.

Infant weight at 12 weeks and 1 year correlated with maternal weight during trimester one for NW and OB groups ($r = 0.25$ [$P =$ 0.015] and $r = 0.31$ [$P = 0.003$], respectively), but not the GDM group.

Glucose and HbA1c levels in trimester three did not correlate with infant weight, length, weight/length, BMI, waist, or hips.

DISCUSSION

This is the first study to our knowledge to measure longitudinal development of body composition in early infancy using the ADP reference method in children born to women with obesity or GDM. We found that girl infants, but not boy infants, exposed to maternal obesity or diabetes during gestation had increased adiposity at both 1 and 12 weeks after birth compared with same-sex infants born to NW mothers. These two groups of girls also had a greater BF% than boy infants born to OB mothers or those with GDM, whereas there were no sex differences in body composition measures among infants born to NW women. When all groups were combined, maternal glucose and HbA1c levels, as well as maternal weight, correlated with BF% and FM in girls alone. Furthermore, weight associations between mother and child were only evident in the normoglycemic NW and OB groups. Therefore, we propose that both maternal glycaemia and obesity during pregnancy are determinants of increased adiposity in infants, especially in girls, with glycemic levels more influential than maternal weight for infants born to women with GDM.

In previous studies, the impact of maternal characteristics on body composition in early infancy has typically been determined at only one time point, usually at birth. As the percentage of body-fat is known to increase rapidly during the first 3 months of life, before stabilizing,[29] this period is believed to be a crucial time for the development of adiposity.[8] Our body-fat data for NW group infants (BF% increase from 13.5% to 24.2% between 1 and 12 weeks) is in good agreement with the one previous study measuring body composition in infants by ADP at similar time points,[6] although in that study the investigators did not compare different maternal populations.

We showed that BF% and FM were higher in infants born to mothers with GDM, with differences evident at both 1 and 12 weeks of life, as compared with NW mothers. When separated

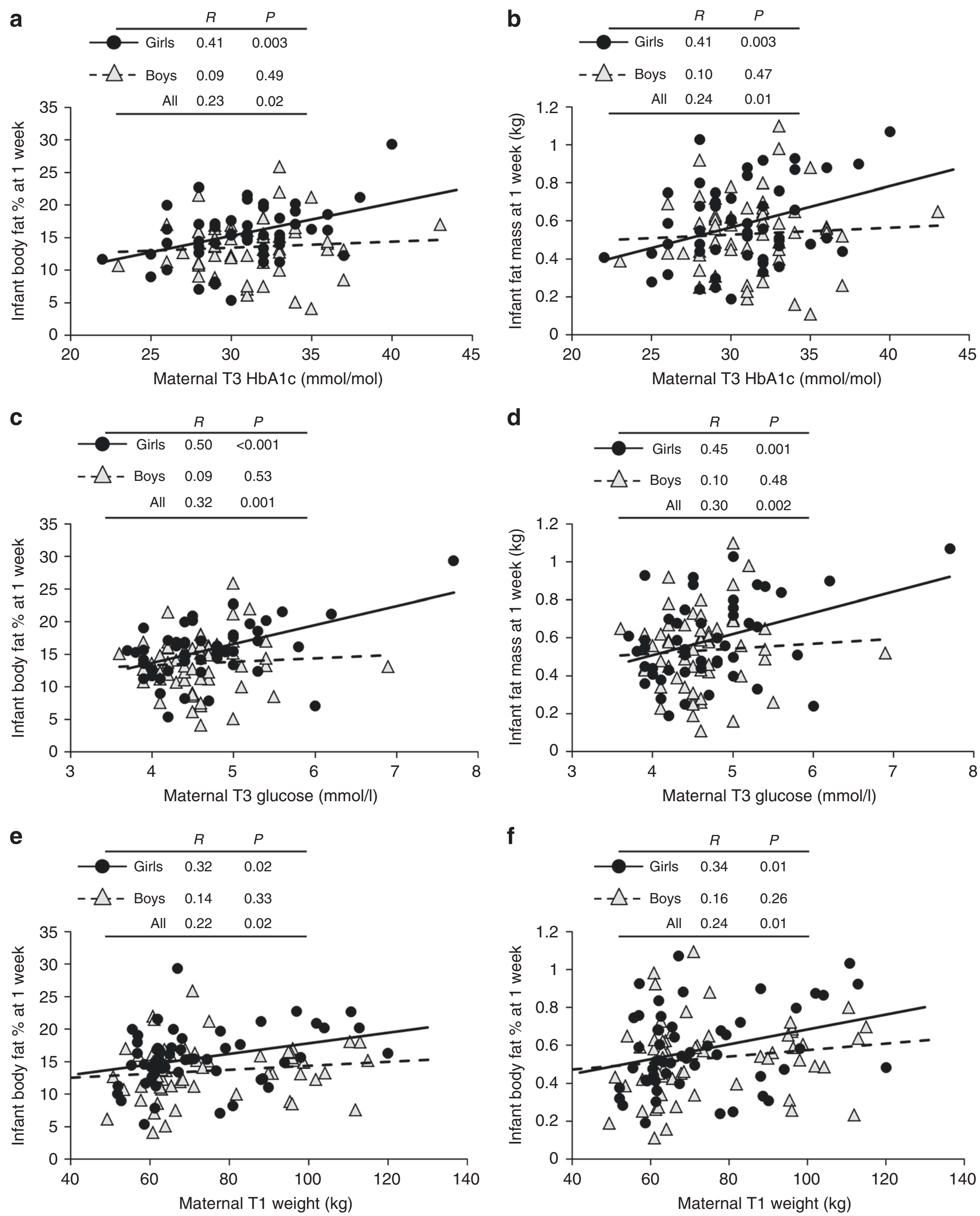

Fig. 3 Correlations of infant body composition and maternal data, grouped by sex. **a**, **b** Maternal HbA1c in trimester three (T3) and infant body-fat percentage (BF%) and fat mass (FM) at 1 week of age. **c**, **d** Maternal glucose in T3 and infant BF% and FM at 1 week of age. **e**, **f** Maternal weight in T1 and infant BF% and FM at 1 week of age. Correlations are adjusted for gestational age and sex; *R* = correlation coefficient; *P* = correlation significance

according to sex, we found that girl infants from both OB and GDM groups had higher BF% and FM than those from the NW group at both time points, but that there were no significant differences for boys. Although some studies have shown that high adiposity at birth, as measured by ADP, is linked to maternal obesity[13] or GDM,[18] few studies have measured later time points, and even fewer have looked at sex differences. Hull et al.[14] found body composition differences between infants from OB and NW women at an average age of 20 days, although the time span of measurement was wide (5–35 days) given the rapid changes in adiposity expected during this time period. The healthy start study[30] measured ADP in 5-month-old infants, and saw correlations between infant FFM (but not FM) and maternal pre-pregnancy BMI, with no correlation when separated by sex. Henriksson at al. measured ADP in 1-week-old infants and established a link between maternal and infant BF% for girls, although few OB mothers were included in the study.[31] Sex differences were also looked at in the Lingwood et al. GDM study, where both infant girls and boys in the GDM group had increased BF% at birth compared with a normoglycemic group.[18] However, girls seemed more influenced by maternal pre-pregnancy BMI and boys by glycemic status. One longer longitudinal study using

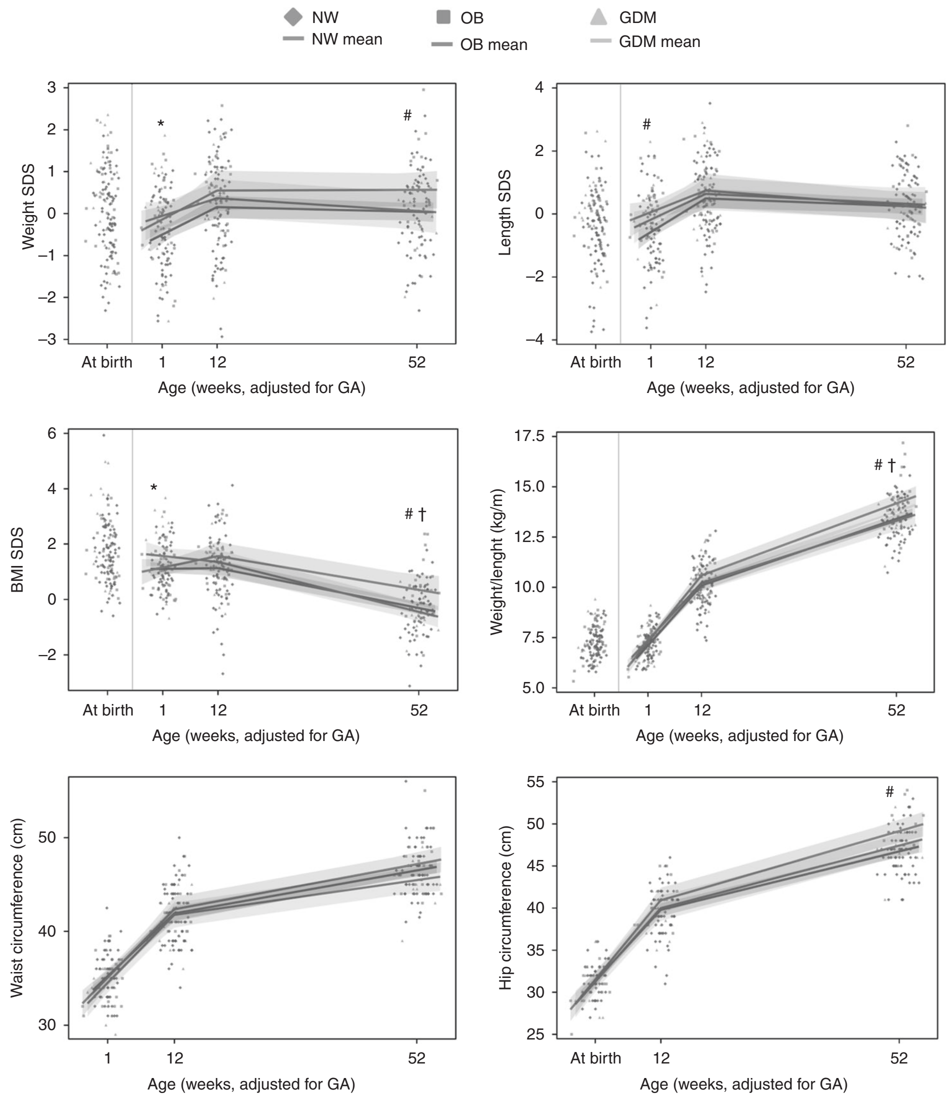

Fig. 4 Longitudinal anthropometric infant growth data from 1 week to 1 year. Individual points and mean ± CI are displayed, where significance ($P < 0.05$) is indicated by *Normal weight (NW) vs. gestational diabetes mellitus (GDM), #NW vs. obese (OB), and †OB vs. GDM. For *p*-values see Supplemental Table S2–S4

DXA saw a higher BF% at 9 and 12 months in girls born to OB mothers compared with girls with overweight or NW mothers, but at later ages (4–6 years), the difference in BF% was most pronounced in boys.[32]

As well as analysing within-sex differences, we also looked at differences in adiposity between girls and boys. There are few reports on differences in body composition between the sexes at this early period of life. However, there have been reports of a higher BF% in girls than boys at birth,[33] at 1 month (but not 3 months) after birth,[29,34] and at 5 months after birth.[30] Interestingly, we found that there was no difference in BF% between girls and boys born to NW women at either 1 or 12 weeks. In infants affected by maternal obesity or diabetes during gestation, however, fairly large differences in BF% were seen between girls and boys at 1 week; a difference that persisted in OB group infants through to 12 weeks of age. This suggests that sex differences may only be apparent in infant populations from mothers of high weight or with dysregulated glucose metabolism.

It is difficult to separate the effects of dysregulated glucose metabolism and obesity, and in our case, to compare the OB and GDM groups. Some OB women inevitably have elevated glucose levels during pregnancy that are not high enough to warrant diagnosis of GDM, and similarly, some women with GDM are also OB. However, when combining all groups in our study, there were significant correlations between maternal HbA1c and fasting glucose levels in late pregnancy and infant BF% and FM at 1 week, highlighting the importance of glycemic status on infant adiposity. When grouped by sex, these correlations only hold true for girl infants, and are especially strong for girls in the GDM group. Our results are in agreement with a study in a non-GDM population where maternal HOMA-IR correlated with FM in infant girls, but not boys, at 1 week of age.[21] On the other hand, Lingwood et al. suggest that maternal blood glucose levels in women with GDM predict adiposity in newborn boys, but not girls.[18] There are differences in study populations and/or time points for blood glucose and body composition measurements between these and our studies, so direct comparisons must be made with caution, and further studies are needed to determine the interaction between infant sex and maternal glucose metabolism. Possible explanations for sex differences seen in our study and others can only be speculated upon. They may be linked to known difference in postnatal sex steroid production during the so called mini-puberty, which could cause sex-specific effects on hormone-sensitive metabolic organs: during the first month of postnatal life,

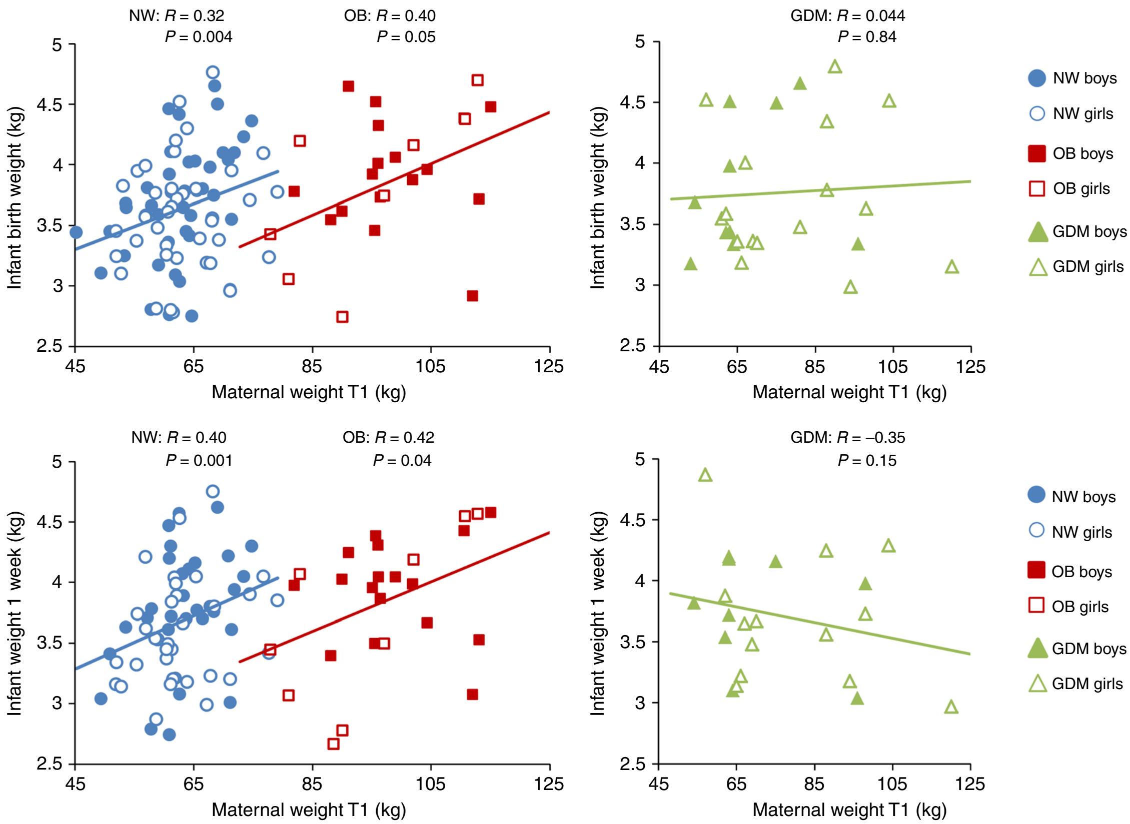

Fig. 5 Correlations between maternal weight at start of pregnancy (T1 trimester one) and infant birthweight or weight at 1 week of age. R correlation coefficient and P correlation significance for partial correlations made separately per group and adjusted for sex and gestational age. GDM gestational diabetes mellitus, NW normal weight, OB obese

boys have a testosterone surge which is linked to increased longitudinal growth, whereas girls have higher levels of oestrogen than boys.[35]

In accordance with the large HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study,[16] we showed that both maternal obesity and GDM resulted in increased birthweight and increased adiposity (as measured with skinfold thickness in the HAPO study). The HAPO study suggests that GDM combined with obesity confers an even greater risk for adverse pregnancy outcomes such as macrosomia than either one alone, although the associations were based on maternal BMI in late gestation. When using pre-pregnancy BMI as an independent factor, associations were reported to be variable. In our study, maternal weight measured during trimester one correlated with infant weight within the NW and OB groups, but not the GDM group, suggesting that glycemic dysregulation rather than maternal weight probably has a greater impact on intrauterine growth in women with GDM.

At 1 year of age, the infants in our study born to OB mothers had increased more in weight, weight/length, and BMI compared with both NW and GDM groups. Interestingly, anthropometric differences between OB and NW group infants at 1 year were only seen in boys, whereas at 12 weeks OB group girls had higher BMI and weight/length. This could be coupled with the Andres et al. study, showing higher BF% in early infancy for girls vs. later infancy for boys, born to OB mothers.[32] However, with no ADP measurement at the 1-year time point in our study, it is difficult to draw conclusions about gains in BF%. BMI is often used as a proxy for body composition, although recent studies have shown that measurements of BMI gain in late infancy have limited use as a surrogate marker for adiposity gain. Longitudinal follow up will be required to assess whether the rapid increase in weight and BMI seen in our infants born to OB mothers predicts later adiposity gain. Looking even further along the lifeline, the Helsinki Birth Cohort Study showed that high maternal BMI was associated with higher BF% at 62 years of age in female offspring only,[36] and that the association between maternal BMI and type 2 diabetes in offspring, was strongest in women.[37] For coronary heart disease, however, the link with high maternal BMI was only significant in males.[6]

The PONCH study is a well-controlled study, including regular visits for both mother and child throughout pregnancy and childhood until 6 years of age. This ensures robust longitudinal data collection at several time points, which is often lacking in other studies of mother–baby dyads. We have used the ADP reference method for body composition measurements, and to ensure that interpretation is meaningful, we have chosen to compare our data with other studies using high-quality, reproducible techniques (ADP or DXA), wherever possible. Due to the complex design of the study it is, however, difficult to include large populations, something that would have been an advantage if wanting to stratify data further, both by group and sex. There could be confounding factors which have not been adjusted for in this study, such as a family history of diabetes or environmental factors. We did, however, not see a difference in infant outcome between those GDM-women with a reported family history of diabetes compared to those GDM mothers with no family history. Further, we did not find differences between groups in reported dietary intake or physical activity during pregnancy. We performed additional analysis adjusting for education or breast-feeding, though chose to present unadjusted data in figures as our main focus was how obesity or GDM affected infant body composition per se. Education was lower in the OB group as expected,[38] and is probably one of the contributing factors that lead to obesity. When adjusting for education, differences between OB and NW were therefore partly cancelled out and led to significance loss in some cases. Adjusting for breastfeeding did not change any of these significances.

In conclusion, risk factors for metabolic dysfunction later in life for infants born to women who were OB or diabetic during pregnancy may already be apparent during the first 3 months of life, with increased adiposity being evident already during this crucial period. Our data point to sexual dimorphism, where adiposity is only affected by high maternal BMI and dysregulated glucose metabolism in infant girls. Maternal glycemic status seems to be of particular relevance for intrauterine growth and increased adiposity in early infancy. However, at 1 year of age, a greater than normal BMI is linked to maternal obesity rather than GDM. Our results add to the accumulating evidence pointing to the importance of interventions before pregnancy to reduce maternal obesity, and the necessity of identifying pregnant women with hyperglycaemia as early as possible in order to establish healthy lifestyle choices and well-controlled glucose levels.

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ADDITIONAL INFORMATION

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