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Abstract

Context

Maternal body mass index (BMI) is associated with increased birth weight but does not explain all the variance in fetal adiposity. Objective

To assess the contribution of maternal body fat distribution to offspring birth weight and adiposity. Design

Longitudinal study throughout gestation and at delivery. Setting

Women recruited at 12 weeks of gestation and followed up at 26 and 36 weeks. Cord blood was collected at delivery. Patients

Pregnant women (n = 45) with BMI 18.0 to 46.3 kg/m^2 and healthy pregnancy outcome. Methods

Maternal first trimester abdominal subcutaneous and visceral adipose tissue thickness (SAT and VAT) was assessed by ultrasound. Main Outcome Measures

Maternal body fat distribution, maternal and cord plasma glucose and lipid concentrations, placental weight, birth weight, and fetal adiposity assessed by cord blood leptin. Results

VAT was the only anthropometric measure independently associated with birth weight centile (r^2 adjusted 15.8%, P = .002). BMI was associated with trimester 2 and trimesters 1 through 3 area under the curve (AUC) glucose and insulin resistance (Homeostatic Model Assessment). SAT alone predicted trimester 2 lipoprotein lipase (LPL) mass (a marker of adipocyte insulin sensitivity) (11.3%, P = .017). VAT was associated with fetal triglyceride (9.3%, P = .047). Placental weight was the only independent predictor of fetal adiposity (48%, P < .001). Maternal trimester 2 and AUC LPL were inversely associated with fetal adiposity (r = -0.69, P = .001 and r = -0.58, P = .006, respectively). Conclusions

Maternal VAT provides additional information to BMI for prediction of birth weight. VAT may be a marker of reduced SAT expansion and increased availability of maternal fatty acids for placental transport.

Keywords

centile, adipose, weight, maternal, birth, prediction, link, missing, expansion, tissue

Disciplines

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Maternal adipose tissue expansion, a missing link in the prediction of birth weight centile

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Keywords: Pregnancy, adipose tissue, birth weight, insulin resistance, body fat distribution

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Abstract

Context Maternal body mass index (BMI) is associated with increased birth weight but does not explain all the variance in fetal adiposity.

Objective To assess the contribution of maternal body fat distribution to offspring birth weight and adiposity.

Design Longitudinal study throughout gestation and at delivery.

Setting Women recruited at 12 weeks of gestation and followed up at 26 and 36 weeks. Cord blood was collected at delivery.

Patients Pregnant women (n=45) with BMI 18.0-46.3 kg/m^2 and healthy pregnancy outcome.

Methods Maternal first trimester abdominal subcutaneous and visceral adipose tissue thickness (SAT and VAT) was assessed by ultrasound.

Main outcome measures Maternal body fat distribution, maternal and cord plasma glucose and lipid concentrations, placental weight, birth weight and fetal adiposity assessed by cord blood leptin.

Results VAT was the only anthropometric measure independently associated with birth weight centile (r^2 adjusted 15.8%, *P*=0.002). BMI was associated with trimester 2 and trimester 1 – 3 area under the curve (AUC) glucose and insulin resistance (HOMA). SAT alone predicted trimester 2 lipoprotein lipase (LPL) mass (a marker of adipocyte insulin sensitivity) (11.3%, *P*=0.017). VAT was associated with fetal triglyceride (9.3%, *P*=0.047). Placental weight was the only independent predictor of fetal adiposity (48%, *P*<0.001). Maternal trimester 2 and AUC LPL were inversely associated with fetal adiposity (r=-0.69, *P*=0.001 and r=-0.58, *P*=0.006 respectively).

Conclusions Maternal VAT provides additional information to BMI for prediction of birth weight. VAT may be a marker of reduced SAT expansion and increased availability of maternal fatty acids for placental transport.

Precis

In pregnant women with a healthy pregnancy outcome, first trimester visceral adipose tissue predicted birthweight centile possibly due to increased delivery of fatty acids to the placenta.

Introduction

Maternal obesity occurs in around 20% of the UK antenatal population (1) and is associated with an increased risk of adverse pregnancy outcome (2) including the metabolic diseases of pregnancy, gestational diabetes mellitus (GDM) and pre-eclampsia. Maternal obesity is also associated with offspring obesity, both at birth and in later life (3). Studies show that maternal pre-pregnancy total body fat predicts birth weight, though it is unclear to what extent this is explained by fetal somatic growth or fetal accumulation of fat (4). There is increasing concern about the impact of maternal BMI on the long term metabolic health of the fetus (5).

Maternal obesity is associated with maternal insulin resistance (6) and metabolic dysfunction (7,8). GDM is defined by maternal hyperglycaemia and the associated fetal macrosomia may be explained by increased placental transport of glucose leading to increased fetal insulin secretion and hence increased growth, as described by Pedersen (9). This observation has now been extended to glucose tolerant mothers, as in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial, which highlighted the importance of maternal plasma glucose concentrations for increased birth weight and adiposity in the offspring (5). However, plasma glucose concentration did not explain all the variance in offspring adiposity, with residual contributions coming from maternal pre-pregnancy BMI and gestational weight gain (10-12). Furthermore, increased birth weight is observed even in GDM pregnancies in which plasma glucose is well-controlled (10,13,14).

There is evidence to suggest that high maternal fat mass and insulin resistance may expose the fetus to fuels other than glucose that could contribute to higher birth weight (13,15-17). Maternal hypertriglyceridaemia is a key element of maternal obesity and insulin resistance (7,8). Whole body lipolysis is increased in the third trimester of pregnancy (18) and is associated with maternal fat mass and estimated fetal weight (19). Maternal plasma triglyceride and free fatty acid also correlate with birth weight and measures of neonatal adiposity in GDM and in women screened for GDM with normal glucose tolerance (20-22). However, it is not clear if these relationships exist in healthy non-obese pregnancy, to what extent they are independent of maternal body weight, and whether measures of maternal body fat distribution may be superior predictors of fetal birth weight and/or adiposity (23).

Obesity, as defined by BMI in excess of 30, is a universally accepted measure of body fatness, but BMI conveys no information about the quantity, quality, location or metabolic function of discrete fat depots. BMI is a relatively weak proxy for discriminating metabolic dysfunction and cardio-metabolic risk in comparison to central obesity, especially when the latter is distinguished by high intra-abdominal visceral adipose tissue (VAT)(24). BMI is unable to distinguish between individuals (pregnant or non-pregnant) who store fat as relatively benign subcutaneous adipose tissue (SAT) or as VAT, which is intimately associated with insulin resistance, hyperglycaemia, hypertriglyceridaemia, metabolic dysfunction and pathology (25-27). None of the above studies that related maternal adiposity to offspring birthweight and adiposity assessed body fat distribution.

In studies of pregnancy that did assess body fat distribution, pre-peritoneal and visceral fat were shown to increase during gestation, while SAT declined (28-32). Measures of VAT strongly predict metabolic complications of pregnancy, GDM (33,34) and pre-eclampsia (35,36), but it is not clear to what extent VAT is directly related to insulin resistance and increased plasma lipids and glucose in pregnancy (33,37-42). While VAT, measured by ultrasound between 12 and 20 weeks of gestation, is associated with fetal growth in overweight and obese women in the first trimester (43), with fetal growth and adiposity in the second trimester (44), and birthweight (45), the impact of abdominal SAT thickness on these measures has been largely overlooked. SAT thickness is correlated with first trimester fetal growth, but less so than VAT (43). SAT has also been found to be predictive (46-48) and non-predictive of GDM (49), and is also less strongly associated with metabolic risk factors in pregnancy than VAT (37).

The aim of this study was to assess the contribution of maternal body fat distribution to offspring birth weight and maternal and fetal insulin resistance in order to advance our understanding of the consequences of maternal obesity. Maternal first trimester measures of adiposity including BMI, VAT, abdominal SAT and hip circumference (a biomarker of lower body SAT) were assessed as predictors of birth weight, adiposity and metabolic dysfunction in neonates of healthy pregnant women. We also determined if any relationship could be explained by the influence of these fat depots on maternal glucose and lipid metabolism or placental weight.

Methods

Longitudinal Study of Pregnancy

Sixty women registered for obstetric care at the Princess Royal Maternity Unit, Glasgow, who were healthy and normotensive with no significant past medical history were recruited and followed prospectively throughout pregnancy. This study was initially designed to assess the impact of maternal obesity on microvascular function and powered for that outcome (50). Seven women were excluded from the final analysis; three delivered pre-term, two were excluded because of missing birth weight data, one had a miscarriage, and one had a baby with diGeorge syndrome. All remaining women had no pregnancy-related complications. Baseline data and complete longitudinal data were available for 53 and 45 women, respectively. The study was performed according to the Declaration of Helsinki, approval was granted by the Research Ethics Committee of North Glasgow University NHS Trust, and each subject gave written informed consent. The women attended after an overnight fast (>10 hours). Blood samples were collected at a mean of 12.4 (range 8–14) [T1], 26.1 (24–28) [T2] and 35.5 (33–38) [T3] weeks of gestation. The characteristics of the patients were recorded at the first antenatal hospital appointment and delivery details from patient notes. Customised birth weight centiles were calculated using the Gestation Network Centile Calculator 5.4 (http://www.gestation.net/birthweight_centiles/centile_online.htm). Deprivation category (DEPCAT score), a measure of socioeconomic status, was assigned using the Scottish Area Deprivation Index for Scottish postcode sectors, 1998 (51). Placental

tissue and fetal cord blood was collected at delivery from a subgroup of these pregnancies (n=23, 42%).

Baseline anthropometric and fat thickness measurements

At the first antenatal appointment (mean 12.4 weeks of gestation), patient height, weight, waist circumference and hip circumference were measured. Waist circumference was measured at the level of the umbilicus. Hip circumference was measured at the widest point over the buttocks. Waist and hip circumference were measured in duplicate to the nearest 0.5 cm. If the difference between the two measurements was greater than 2 cm, a third measurement was taken and the mean of the two closest measurements was calculated. All measurements were taken by the same examiner. Body mass index (BMI) was calculated as booking weight (kg), divided by height (m) squared. Baseline upper body abdominal SAT and upper body VAT thickness was assessed by ultrasound (52). Measurements were taken 2cm below the xiphisternum and the abdominal probe was placed on the skin with minimal pressure. Abdominal SAT was measured as the thickness between the inferior border of the dermal layer and the rectus abdominus sheath at the level of the umbilicus. Visceral fat was taken as the vertical measurement between the rectus sheath and the aorta at the umbilicus. Three consecutive measurements in millimetres were taken and an average reading was calculated. All measures were made by the same operator (F.S.) on the same machine.

Blood parameters

Glucose assays (53) were performed by Clinical Biochemistry, Glasgow Royal Infirmary and plasma total cholesterol, HDL cholesterol and total triglyceride concentrations were determined as described previously (7). Insulin (Mercodia) and leptin (R & D Systems) analyses were performed by ELISA according to the manufacturer's instructions. LPL mass was determined by ELISA using bovine LPL as standard (54,55). HOMA was calculated as [fasting insulin (mU/L) x fasting glucose (mmol/L)]/22.5]. Erythrocyte membrane phospholipid fatty acid composition was measured as previously described (56), and the ratio of 16:0/18:2 n-6 was used as an index of *de novo* lipogenesis (57,58).

Statistical analysis

Continuous variables are represented as means (standard deviation), categorical variables as number and percentage. Total area under the time (T1 to T3 weeks' gestation) x concentration curve (AUC) were calculated using the trapezium method (59). Normality testing was carried out using the Ryan-Joiner test and data was log or square root transformed to achieve a normal distribution as necessary. Associations between variables were examined by Pearson's correlation analysis. Two measures of gestational fuel exposure were used. Firstly, the total area under the trimester 1 to trimester 3 maternal glucose, and triglyceride concentration and HOMA curves were calculated to assess total gestational exposure. Secondly, because the univariate associations between maternal anthropometrics and maternal plasma triglyceride, glucose and HOMA were the strongest and notably distinct in trimester 2 (Supplemental Figure 1(60)), trimester 2 data were selected for further study.

Stepwise regression analysis, a method of fitting regression models in which the choice of predictive variables and simultaneous removal of unimportant variables is carried out by an automatic procedure, was used to test associations between maternal anthropometrics and maternal or fetal blood glucose and lipids and the influence of confounding variables such as placental weight, using *P*-to-enter and *P*-to-stay $P<0.15$. All statistical analysis was carried out in Minitab Vs18.

Results

Maternal characteristics

Demographic data for all women with first trimester measurements are shown in Table 1. Women were on average 28 years of age, had a mean body mass index (BMI) of 28 kg/m^2; just over one third were currently smoking during their pregnancy and just less than one half were in their first pregnancy. More than half the women were classed as having deprived social status. The women had normal antenatal appointment blood pressure, had no pregnancy-related complications and all delivered healthy babies at term. The demographic characteristics of the subgroup, where repeated longitudinal measures were available, were similar to the total group (Table 1).

Relationship between maternal anthropometrics and offspring birth weight centile and placental weight

Maternal BMI is a recognised predictor of offspring birthweight. To test whether other, more specific, measures of maternal adiposity might be better predictors of offspring birth weight, univariate correlation between maternal anthropometric measures and birth weight centile, birth weight and placental weight were first assessed. Birth weight centile was associated with maternal BMI (r=0.41, *P*=0.002), waist circumference (r=0.42, *P*=0.003), hip circumference (r=0.32, *P*=0.021), SAT thickness (r=0.34, *P*=0.012), VAT thickness (r=0.41, *P*=0.003) and SAT plus VAT thickness (r=0.39, *P*=0.004), but not waist-hip ratio (r= 0.16, *P*=0.25) or VAT/SAT ratio (r=0.01, *P*=0.97). No maternal anthropometric measures were associated with birth

weight alone, and only maternal BMI was weakly associated with placental weight (r=0.27, *P*=0.047).

To examine possible multivariable associations between maternal anthropometrics and birth weight centile, the former was entered into a stepwise regression model (*P* to enter and *P* to stay 0.15). VAT was the only anthropometric measure significantly associated with birth weight centile (r^2 adjusted 15.8%, *P*=0.002, Figure 1). A one mm increase in VAT thickness resulted in a 2.26 centile increase in birthweight centile. A VAT thickness of up to 10mm was associated with the 43rd (unadjusted) and 38th (after adjustment for BMI, waist circumference, hip circumference, SAT thickness and SAT plus VAT thickness) birth weight centile. Above 10mm VAT, birth weight centiles were between the 70th and 80th centile. While inclusion of placental weight in the regression model attenuated the relationship between VAT and birth weight centile, it remained significant [r^2 adjusted 11.8%, *P*=0.006; birth weight centile = -12.3 + 1.891 VAT (mm) + 0.0630 placental weight (g)] suggesting an independent association between VAT thickness and birth weight centile. Placental weight was significantly associated with birth weight centile in this model (r^2 adjusted 12.1%, *P*=0.005), suggesting that placental weight also has an independent contribution to birth weight equivalent to that of VAT thickness.

Relationships between maternal anthropometrics and fetal cord plasma glucose and lipids

In a univariate analysis maternal VAT thickness was significantly correlated (*P*<0.05) with fetal cord plasma total cholesterol, triglyceride, non-esterified fatty acids and negatively with a marker of insulin resistance (HOMA), but there was no relationship

with fetal cord plasma HDL cholesterol, glucose or insulin (Table 2). Maternal SAT thickness correlated significantly with cord plasma total cholesterol. There was no relationship between maternal BMI or hip circumference and cord plasma glucose or lipids. On multivariate regression analysis, VAT showed significant independent associations with cord plasma triglyceride, non-esterified fatty acids and cholesterol, while BMI showed significant negative independent associations with cord plasma insulin and HOMA (Table 2). After inclusion of mode of delivery in the model, the associations between maternal BMI and cord plasma insulin and HOMA and between VAT and cord plasma triglyceride persisted and now hip circumference was positively associated with cord plasma cholesterol (Table 2). The inclusion of placental weight in the regression model had no impact on the associations between BMI and cord plasma HOMA, VAT thickness and cord plasma triglyceride or between hip circumference and cord plasma cholesterol maternal BMI and HOMA. The inclusion of placental weight strengthened the negative association between BMI and cord blood insulin (r^2 adjusted 31%, P=0.009).

Relationship between maternal anthropometrics and maternal plasma glucose and lipids

Maternal BMI was correlated significantly (P<0.05) with maternal trimester 2 and AUC glucose and trimester 2 and AUC HOMA (Table 3). SAT thickness was correlated significantly with maternal trimester 2 HOMA only. VAT thickness was correlated with maternal trimester 2 glucose and HOMA. Hip circumference was correlated with maternal AUC glucose and trimester 2 and AUC HOMA. On stepwise regression,

only maternal BMI remained significantly associated with both maternal trimester 2 and AUC glucose and HOMA (Table 3).

Relationships between maternal plasma glucose and lipid exposure and fetal cord plasma glucose and lipids, fetal adiposity (cord plasma leptin) and birth weight centile

None of the markers of maternal glucose or lipid gestational exposure were associated with any measure of cord plasma glucose or lipid metabolism or fetal adiposity before or after accounting for mode of delivery other than maternal AUC triglyceride (r^2 = 20%, *P*=0.020, coefficient = -0.007) and maternal AUC HOMA (r^2=15%, *P*=0.042, coefficient = 0.255) which were associated with cord plasma HDL after accounting for mode of delivery. Maternal trimester 2 HOMA (r=0.33, *P*=0.028) and AUC glucose (r=0.36, *P*=0.016) were univariately associated with birthweight centile. T2 HOMA (*P*=0.046) and placental weight (*P*<0.001) remained as predictors of birthweight centile in a minimal model that included these two variables and AUC glucose (r^2 adjusted =31.7%).

Maternal anthropometric measures and fetal adiposity

Fetal adiposity was not associated with maternal BMI, SAT or VAT thickness or hip circumference in multivariate analysis. However, there was a significant positive association between placental weight and cord plasma leptin (r^2=57%, *P*<0.001). A multivariable model including maternal anthropometrics, placental weight and mode of delivery showed that only placental weight was independently associated with fetal adiposity (r^2 adjusted 48%, *P*<0.001). There was no association between cord

plasma triglyceride or non-esterified fatty acids and fetal adiposity even after adjusting for mode of delivery. The 16:0/18:2 n-6 ratio of fetal erythrocyte fatty acids was used as an index of *de novo* lipogenesis. This index was unrelated to fetal adiposity (r=-0.13, *P*=0.57), but inversely associated with fetal cord plasma triglyceride (r=-0.44, *P*=0.044) (Supplemental Figure 2 (60)), an effect lost after accounting for mode of delivery.

Maternal lipoprotein lipase (LPL) mass, maternal and fetal plasma glucose and lipids, fetal adiposity and birth weight centile

Low LPL mass is a marker of severity of metabolic syndrome and low plasma levels reflect reduced LPL synthesis by adipocytes in the insulin resistant state. Maternal trimester 2 LPL mass was negatively correlated with maternal BMI (r=-0.36, *P*=0.017) and SAT (r=-0.36, *P*=0.018) while AUC LPL mass correlated with SAT (r=-0.30, *P*=0.048). In a multivariate regression model including all maternal anthropometrics, maternal SAT alone predicted trimester 2 LPL mass (r^2 adjusted 11.3%, *P*=0.017). Maternal trimester 2 or AUC LPL mass was not correlated with cord plasma glucose or lipid levels. Maternal trimester 2 LPL was negatively correlated with maternal trimester 2 glucose (r=-0.30, *P*=0.049), AUC glucose (r=-0.36, *P*=0.019) and trimester 2 HOMA (-0.30, *P*=0.048). In particular, maternal trimester 2 and AUC LPL mass were strongly correlated with maternal trimester 2 triglycerides (r=-0.52, *P*=0.001 and r=-0.55, *P*<0.001 respectively) and AUC triglycerides (r=-0.41, *P*=0.007 and r=-0.41, *P*=0.006 respectively). Maternal trimester 2 and AUC LPL were not associated with birth weight centile but both were strongly associated with fetal leptin (r=-0.69,

P=0.001 and r=-0.58, *P*=0.006 respectively) (Figure 2) and these associations were independent of mode of delivery.

Discussion

Maternal first trimester VAT thickness on ultrasound, but not first trimester BMI, abdominal SAT or hip circumference, was independently associated with birth weight centile. This observation is in agreement with a similar study in adolescent mothers, although the previous study lacked SAT assessment (45). The strength of associations in the current study were of greater magnitude than that previously reported, possibly due to our older, more obese population. Maternal VAT was also associated with fetal cord plasma triglyceride although the latter variable was unrelated to birth weight centile or fetal adiposity. Maternal VAT was not associated with maternal plasma lipids, as might be expected from data in non-pregnant women, in which an oversupply of fatty acids in the portal circulation to the liver can drive an increased synthesis and secretion of VLDL (61). This lack of relationship between maternal VAT and plasma triglyceride suggests that VAT-associated hypertriglyceridaemia may be superseded by maternal metabolic adaptation to pregnancy.

We have previously shown in *ex vivo* adipocyte lipolysis experiments, that SAT adipocytes have higher lipolysis rates than VAT adipocytes in pregnancy (62). Thus, in healthy pregnancy, SAT rather than VAT is the primary source of the maternal fatty acids released for maternal metabolism and placental transport, secondary to pregnancy hormone induced gestational insulin resistance (62). A slowing or reversal of maternal (subcutaneous) adipose tissue accumulation towards the end of the second trimester coincides with the accelerated phase of fetal adipose tissue

accretion (14). In pregnancy, it is possible that VAT is a marker of ectopic fat accumulation rather than a direct source of lipids for transport to the fetus. In non-pregnant individuals, fat accumulation in VAT and ectopically in other organs is secondary to dysregulated adipocyte expansion in subcutaneous fat (24,63,64). Fatty acids that overspill from the SAT compartment accumulate in VAT and are stored ectopically as intracellular lipid droplets in other tissues such as the liver and pancreas. However, in pregnancy, the overspill fatty acids from SAT could also be available for uptake and transport by the placenta, thus increasing lipid supply to the fetus (Figure 3).

Low maternal LPL mass is a measure of metabolic syndrome severity and probably reflects a reduced rate of LPL synthesis by insulin resistant SAT adipocytes (7,65-67). In the present study, LPL mass was inversely associated with maternal plasma triglyceride and fetal adiposity, supporting the idea of a failure of SAT adipocyte expansion and the development of adipocyte insulin resistance with a consequent overspill of fatty acids and transport to the fetus (Figure 3). Potential mechanisms for increased fetal adiposity include an increased lipid supply across the placenta or increased *de novo* lipogenesis from glucose supplied across the placenta. The inverse association between cord plasma triglyceride and an index of fetal *de novo* lipogenesis was not independent of mode of delivery, and in any case would suggest that the transported fatty acids may be utilised by the fetus in preference to the *de novo* synthesis of fatty acids. Failure of SAT adipocyte expansion has been proposed to underlie obesity-related pre-eclampsia (62) and gestational diabetes mellitus (68,69). In the healthy women under study here, the maximum VAT thickness

measured was 27.3mm, which may represent a propensity towards limited SAT expansion rather than a pathological state, especially when it is considered that preliminary studies indicated that pre-eclampsia and GDM are predicted by VAT thickness above 52mm (36) and 47.4mm (33) respectively. Assessment of VAT thickness in larger populations would be useful to assess its ability to predict similar adverse pregnancy outcomes.

Maternal placental weight had an independent association with birth weight centile in this cohort of women. Maternal body mass index was related to both placental weight and maternal insulin resistance, and through these associations may be indirectly linked to birth weight centile and fetal adiposity. Our data showed that trimester 2 markers of glucose metabolism were most strongly related to maternal anthropometrics. The middle trimester is the time of greatest acceleration in fetal growth (70), when changes in maternal metabolism would be expected to have most impact on birthweight centile. Maternal gestational insulin resistance directs more glucose for transport to the fetus. A combination of higher placental weight, increased surface area for transport of nutrients, and raised trimester 2 plasma glucose may explain the link between BMI and fetal birth weight centile and adiposity. Interestingly, maternal BMI was associated with reduced fetal cord blood insulin and HOMA suggesting that in the present study fetuses of healthy high BMI mothers are more insulin sensitive and hence efficient at storing fuel as adipose tissue in addition to having more insulin-induced somatic growth. However, this could be due to our small sample size and limited statistical ability to account for confounders. Previous larger studies (5,71) show a positive relationship between

maternal BMI and cord blood insulin suggesting that Pedersen's hypothesis also applies in healthy normoglycaemic pregnancies. It is currently not clear to what extent fetal insulin sensitivity is directly influenced by the mother or is a fetal response to the availability of fuel.

The data presented here suggest an input from both glucose and lipids into birth weight and fetal adiposity. While there is plentiful evidence to link maternal plasma glucose levels with fetal growth, there has been less research into the role of plasma lipids. Lipid concentrations are equally regulated by insulin and affected by insulin resistance. It is notable that a stable isotope tracer study in healthy women at 34-36 weeks of gestation showed that both glucose production rate and lipolysis were independently correlated with estimated fetal size on ultrasound scan (19). Our data also suggest that glucose and lipid metabolism are intertwined and influenced by both maternal adiposity and body fat distribution.

This study had a number of strengths including its prospective design and the assessment of a number of maternal anthropometrics in parallel with measures of both maternal and fetal cord glucose and lipid metabolism. Limitations include a lack of kinetic assessment of maternal and fetal metabolites and the use of steady state concentrations to infer such fluxes. Our conclusions with respect to fetal adiposity are limited by cord blood samples being collected in less than half of the cohort (23 pregnancies), in which plasma leptin concentration was measured as a surrogate. In addition, cord plasma measurements may have been confounded by a number of pregnancy factors including fetal sex, mode of delivery, gestational age and maternal

fasting status at delivery and maternal smoking, statistical adjustment for which may have been inadequate

In summary, maternal body fat distribution in healthy pregnancy, as identified by VAT thickness, provides additional information to that of maternal BMI in the prediction of birth weight centile. VAT may be acting as a marker of reduced SAT expansion, leading to increased availability of plasma fatty acids for placental transport. The data do not address the clinical value of measuring SAT and VAT over BMI as ultimately the data do not directly link either SAT or VAT to any adverse maternal or fetal pregnancy outcome. Instead the data suggest that the ability of a woman to expand her SAT depot in response to pregnancy hyperphagia may predict her metabolic response and ultimately her susceptibility to metabolic complications of pregnancy, such as pre-eclampsia and GDM, and her offspring's propensity to adiposity, at least at birth. As to what is the best marker of this susceptibility e.g. VAT depot size or plasma LPL mass is not currently clear, but worth exploring in the future.

Data availability

The datasets generated during and analysed during the current study are not publically available but are available from the corresponding author on reasonable request.

References

1. Centre for Maternal Child Enquiries. Maternal obesity in the UK: Findings from a national project. *London: Centre for Maternal and Child Enquiries*2010.
2. Jarvie E, Ramsay JE. Obstetric management of obesity in pregnancy. *Seminars in fetal & neonatal medicine*. 2010;15(2):83-88.
3. Catalano PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. *Journal of developmental origins of health and disease*. 2010;1(4):208-215.
4. Forsum E, Lof M, Olausson H, Olhager E. Maternal body composition in relation to infant birth weight and subcutaneous adipose tissue. *The British journal of nutrition*. 2006;96(2):408-414.
5. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009;58(2):453-459.
6. Lain KY, Catalano PM. Factors that affect maternal insulin resistance and modify fetal growth and body composition. *Metabolic syndrome and related disorders*. 2006;4(2):91-100.
7. Meyer BJ, Stewart FM, Brown EA, Cooney J, Nilsson S, Olivecrona G, Ramsay JE, Griffin BA, Caslake MJ, Freeman DJ. Maternal obesity is associated with the formation of small dense LDL and hypoadiponectinemia in the third trimester. *The Journal of clinical endocrinology and metabolism*. 2013;98(2):643-652.
8. Ramsay JE, Ferrell WR, Crawford L, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *The Journal of clinical endocrinology and metabolism*. 2002;87(9):4231-4237.
9. Pedersen J. The pregnant diabetic and her newborn: Problems and management. . William & Wilkins; Baltimore, MD.
10. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG : an international journal of obstetrics and gynaecology*. 2010;117(5):575-584.
11. Badon SE, Dyer AR, Josefson JL. Gestational weight gain and neonatal adiposity in the Hyperglycemia and Adverse Pregnancy Outcome study-North American region. *Obesity (Silver Spring, Md)*. 2014;22(7):1731-1738.
12. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, Lowe LP, Trimble ER, Coustan DR, Hadden DR, Persson B, Hod M, Oats JJ. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes care*. 2012;35(4):780-786.
13. Ong KK, Diderholm B, Salzano G, Wingate D, Hughes IA, MacDougall J, Acerini CL, Dunger DB. Pregnancy insulin, glucose, and BMI contribute to birth outcomes in nondiabetic mothers. *Diabetes care*. 2008;31(11):2193-2197.
14. Haggarty P. Fatty acid supply to the human fetus. *Annual review of nutrition*. 2010;30:237-255.
15. Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? *American journal of obstetrics and gynecology*. 2011;204(6):479-487.

16. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*. 1980;29(12):1023-1035.
17. Scholtens DM, Bain JR, Reisetter AC, Muehlbauer MJ, Nodzenski M, Stevens RD, Ilkayeva O, Lowe LP, Metzger BE, Newgard CB, Lowe WL, Jr. Metabolic Networks and Metabolites Underlie Associations Between Maternal Glucose During Pregnancy and Newborn Size at Birth. *Diabetes*. 2016;65(7):2039-2050.
18. Diderholm B, Stridsberg M, Ewald U, Lindeberg-Norden S, Gustafsson J. Increased lipolysis in non-obese pregnant women studied in the third trimester. *BJOG : an international journal of obstetrics and gynaecology*. 2005;112(6):713-718.
19. Diderholm B, Beardsall K, Murgatroyd P, Lees C, Gustafsson J, Dunger D. Maternal rates of lipolysis and glucose production in late pregnancy are independently related to foetal weight. *Clinical endocrinology*. 2017;87(3):272-278.
20. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG, Cuccuru I, Pellegrini G, Chatzianagnostou K, Boldrini A, Del Prato S. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. *Diabetic medicine : a journal of the British Diabetic Association*. 2005;22(1):21-25.
21. Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, Herrera E. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. *Diabetes care*. 2008;31(9):1858-1863.
22. Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. *Acta Obstet Gynecol Scand*. 2010;89(5):700-704.
23. Knopp RH, Magee MS, Walden CE, Bonet B, Benedetti TJ. Prediction of infant birth weight by GDM screening tests. Importance of plasma triglyceride. *Diabetes care*. 1992;15(11):1605-1613.
24. Neeland IJ, Ross R, Despres JP, Matsuzawa Y, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB, Griffin B, Zambon A, Barter P, Fruchart JC, Eckel RH. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *The lancet Diabetes & endocrinology*. 2019.
25. Neeland IJ, Ayers CR, Rohatgi AK, Turer AT, Berry JD, Das SR, Vega GL, Khera A, McGuire DK, Grundy SM, de Lemos JA. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity (Silver Spring, Md)*. 2013;21(9):E439-447.
26. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, Balletshofer B, Machicao F, Fritsche A, Haring HU. Identification and characterization of metabolically benign obesity in humans. *Archives of internal medicine*. 2008;168(15):1609-1616.
27. Gast KB, Smit JW, den Heijer M, Middeldorp S, Rippe RC, le Cessie S, de Koning EJ, Jukema JW, Rabelink TJ, de Roos A, Rosendaal FR, de Mutsert R. Abdominal adiposity largely explains associations between insulin resistance, hyperglycemia and subclinical atherosclerosis: the NEO study. *Atherosclerosis*. 2013;229(2):423-429.

28. Kinoshita T, Itoh M. Longitudinal variance of fat mass deposition during pregnancy evaluated by ultrasonography: the ratio of visceral fat to subcutaneous fat in the abdomen. *Gynecologic and obstetric investigation*. 2006;61(2):115-118.
29. Dutra LP, Cisneiros RM, Souza AS, Diniz CP, Moura LA, Figueiroa JN, Alves JG. Longitudinal variance of visceral fat thickness in pregnant adolescents. *Aust N Z J Obstet Gynaecol*. 2014;54(1):91-93.
30. Kennedy N, Quinton A, Brown C, Peek MJ, Benzie R, Nanan R. Changes in maternal abdominal subcutaneous fat layers using ultrasound: A longitudinal study. *Obesity research & clinical practice*. 2017;11(6):655-664.
31. Selovic A, Sarac J, Missoni S. Changes in adipose tissue distribution during pregnancy estimated by ultrasonography. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2016;29(13):2131-2137.
32. Straughen JK, Trudeau S, Misra VK. Changes in adipose tissue distribution during pregnancy in overweight and obese compared with normal weight women. *Nutrition & diabetes*. 2013;3:e84.
33. Martin AM, Berger H, Nisenbaum R, Lausman AY, MacGarvie S, Crerar C, Ray JG. Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. *Diabetes care*. 2009;32(7):1308-1310.
34. Maitland RA, Seed PT, Briley AL, Homsy M, Thomas S, Pasupathy D, Robson SC, Nelson SM, Sattar N, Poston L. Prediction of gestational diabetes in obese pregnant women from the UK Pregnancies Better Eating and Activity (UPBEAT) pilot trial. *Diabetic medicine : a journal of the British Diabetic Association*. 2014;31(8):963-970.
35. Sattar N, Clark P, Holmes A, Lean ME, Walker I, Greer IA. Antenatal waist circumference and hypertension risk. *Obstetrics and gynecology*. 2001;97(2):268-271.
36. Ray JG, De Souza LR, Park AL, Connelly PW, Bujold E, Berger H. Preeclampsia and Preterm Birth Associated With Visceral Adiposity in Early Pregnancy. *J Obstet Gynaecol Can*. 2017;39(2):78-81.
37. Bartha JL, Marin-Segura P, Gonzalez-Gonzalez NL, Wagner F, Aguilar-Diosdado M, Hervias-Vivancos B. Ultrasound evaluation of visceral fat and metabolic risk factors during early pregnancy. *Obesity (Silver Spring, Md)*. 2007;15(9):2233-2239.
38. De Souza LR, Berger H, Retnakaran R, Maguire JL, Nathens AB, Connelly PW, Ray JG. First-Trimester Maternal Abdominal Adiposity Predicts Dysglycemia and Gestational Diabetes Mellitus in Midpregnancy. *Diabetes care*. 2016;39(1):61-64.
39. De Souza LR, Berger H, Retnakaran R, Vlachou PA, Maguire JL, Nathens AB, Connelly PW, Ray JG. Hepatic fat and abdominal adiposity in early pregnancy together predict impaired glucose homeostasis in mid-pregnancy. *Nutrition & diabetes*. 2016;6(9):e229.
40. Duran M, Kosus A, Kosus N, Turhan N. CRP, HbA1c, lipid, and biochemical parameters and their relation with maternal visceral adipose tissue and subcutaneous fat tissue thickness. *Turkish journal of medical sciences*. 2016;46(1):6-12.

41. Ingram KH, Hunter GR, James JF, Gower BA. Central fat accretion and insulin sensitivity: differential relationships in parous and nulliparous women. *International journal of obesity (2005)*. 2017;41(8):1214-1217.
42. Pontual AC, Figueiroa JN, De Souza LR, Ray JG, Alves JG. Visceral Adiposity in the First Half of Pregnancy in Association with Glucose, Lipid and Insulin Profiles in Later Pregnancy: A Cohort Study. *Maternal and child health journal*. 2016;20(8):1720-1725.
43. Selovic A, Belci D. Influence of distribution of mother's abdominal body fat on first trimester fetal growth. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2018:1-6.
44. Lopes KRM, Souza ASR, Figueiroa JN, Alves JGB. Correlation between pre-pregnancy body mass index and maternal visceral adiposity with fetal biometry during the second trimester. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2017;138(2):133-137.
45. Cisneiros RM, Dutra LP, Silveira FJ, Souza AR, Marques M, Amorim MM, Urquia ML, Ray JG, Alves JG. Visceral adiposity in the first half of pregnancy predicts newborn weight among adolescent mothers. *J Obstet Gynaecol Can*. 2013;35(8):704-709.
46. Kennedy NJ, Peek MJ, Quinton AE, Lanzarone V, Martin A, Benzie R, Nanan R. Maternal abdominal subcutaneous fat thickness as a predictor for adverse pregnancy outcome: a longitudinal cohort study. *BJOG : an international journal of obstetrics and gynaecology*. 2016;123(2):225-232.
47. Sommer C, Jenum AK, Waage CW, Morkrid K, Sletner L, Birkeland KI. Ethnic differences in BMI, subcutaneous fat, and serum leptin levels during and after pregnancy and risk of gestational diabetes. *Eur J Endocrinol*. 2015;172(6):649-656.
48. Yang SH, Kim C, An HS, An H, Lee JS. Prediction of Gestational Diabetes Mellitus in Pregnant Korean Women Based on Abdominal Subcutaneous Fat Thickness as Measured by Ultrasonography. *Diabetes & metabolism journal*. 2017;41(6):486-491.
49. Bourdages M, Demers ME, Dube S, Gasse C, Girard M, Boutin A, Ray JG, Bujold E, Demers S. First-Trimester Abdominal Adipose Tissue Thickness to Predict Gestational Diabetes. *J Obstet Gynaecol Can*. 2018;40(7):883-887.
50. Stewart FM, Freeman DJ, Ramsay JE, Greer IA, Caslake M, Ferrell WR. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. *The Journal of clinical endocrinology and metabolism*. 2007;92(3):969-975.
51. Carstairs V, Morris R. Deprivation and mortality: an alternative to social class? *Community medicine*. 1989;11(3):210-219.
52. Armellini F, Zamboni M, Rigo L, Todesco T, Bergamo-Andreis IA, Procacci C, Bosello O. The contribution of sonography to the measurement of intra-abdominal fat. *Journal of clinical ultrasound : JCU*. 1990;18(7):563-567.
53. Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe GD. Lipoprotein-associated phospholipase A2 as an independent predictor of

coronary heart disease. West of Scotland Coronary Prevention Study Group. *The New England journal of medicine*. 2000;343(16):1148-1155.
54. Tornvall P, Olivecrona G, Karpe F, Hamsten A, Olivecrona T. Lipoprotein lipase mass and activity in plasma and their increase after heparin are separate parameters with different relations to plasma lipoproteins. *Arterioscler Thromb Vasc Biol*. 1995;15(8):1086-1093.
55. Vilella E, Joven J, Fernandez M, Vilaro S, Brunzell JD, Olivecrona T, Bengtsson-Olivecrona G. Lipoprotein lipase in human plasma is mainly inactive and associated with cholesterol-rich lipoproteins. *Journal of lipid research*. 1993;34(9):1555-1564.
56. Stewart F, Rodie VA, Ramsay JE, Greer IA, Freeman DJ, Meyer BJ. Longitudinal assessment of erythrocyte fatty acid composition throughout pregnancy and post partum. *Lipids*. 2007;42(4):335-344.
57. Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. *The Journal of clinical investigation*. 1996;97(9):2081-2091.
58. Sweeney MJ, Etteldorf JN, Throop LJ, Timma DL, Wrenn EL. Diet and fatty acid distribution in subcutaneous fat and in the cholesterol-triglyceride fraction of serum of young infants. *The Journal of clinical investigation*. 1963;42:1-9.
59. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ (Clinical research ed)*. 1990;300(6719):230-235.
60. Jarvie EM, Stewart FM, Ramsay JE, Brown EA, Meyer BJ, Olivecrona G, Griffin BA, Freeman DJ. Data from: Maternal adipocyte expansion, a missing link in the prediction of birth weight centile. University of Glasgow, Enlighten: Research Data 2019, Deposited 22nd November 2019 https://doi.org/10.5525/gla.researchdata.915.
61. Veilleux A, Caron-Jobin M, Noel S, Laberge PY, Tchernof A. Visceral adipocyte hypertrophy is associated with dyslipidemia independent of body composition and fat distribution in women. *Diabetes*. 2011;60(5):1504-1511.
62. Huda SS, Forrest R, Paterson N, Jordan F, Sattar N, Freeman DJ. In preeclampsia, maternal third trimester subcutaneous adipocyte lipolysis is more resistant to suppression by insulin than in healthy pregnancy. *Hypertension*. 2014;63(5):1094-1101.
63. Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U. Insulin resistance and impaired adipogenesis. *Trends in endocrinology and metabolism: TEM*. 2015;26(4):193-200.
64. McLaughlin T, Lamendola C, Coghlan N, Liu TC, Lerner K, Sherman A, Cushman SW. Subcutaneous adipose cell size and distribution: relationship to insulin resistance and body fat. *Obesity (Silver Spring, Md)*. 2014;22(3):673-680.
65. Ong JM, Kirchgessner TG, Schotz MC, Kern PA. Insulin increases the synthetic rate and messenger RNA level of lipoprotein lipase in isolated rat adipocytes. *The Journal of biological chemistry*. 1988;263(26):12933-12938.
66. Semenkovich CF, Wims M, Noe L, Etienne J, Chan L. Insulin regulation of lipoprotein lipase activity in 3T3-L1 adipocytes is mediated at posttranscriptional and posttranslational levels. *The Journal of biological chemistry*. 1989;264(15):9030-9038.
67. Saiki A, Oyama T, Endo K, Ebisuno M, Ohira M, Koide N, Murano T, Miyashita Y, Shirai K. Preheparin serum lipoprotein lipase mass might be a

biomarker of metabolic syndrome. *Diabetes Res Clin Pract*. 2007;76(1):93-101.
68. Rojas-Rodriguez R, Lifshitz LM, Bellve KD, Min SY, Pires J, Leung K, Boeras C, Sert A, Draper JT, Corvera S, Moore Simas TA. Human adipose tissue expansion in pregnancy is impaired in gestational diabetes mellitus. *Diabetologia*. 2015;58(9):2106-2114.
69. Tumurbaatar B, Poole AT, Olson G, Makhlouf M, Sallam HS, Thukuntla S, Kankanala S, Ekhaese O, Gomez G, Chandalia M, Abate N. Adipose Tissue Insulin Resistance in Gestational Diabetes. *Metabolic syndrome and related disorders*. 2017;15(2):86-92.
70. Sibley CP, S. DS, J. G, S. G. Relevance of placental transfer to normal and abnormal fetal develpoment. In: Kingdom J, E. J, S OB, eds. The Placenta: Basic Science and Clinical Practice. London, UK: Royal College of Obstetricians and Gynaecologists; 2000:40-50.
71. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes care*. 2009;32(6):1076-1080.

Legends for figures and tables

Figure 1. Offspring birth weight centile by VAT thickness: 0-10mm [n=19, mean (standard deviation) 7.5 (2.0) mm], 10-20mm [n=27, 15.0 (2.6) mm], 20-30mm [n=7, 22.9 (2.9) mm]. Means and 95% confidence interval for the mean are plotted for unadjusted data and data adjusted for other anthropometric measures in a stepwise regression (BMI, waist circumference, hip circumference, SAT thickness, SAT plus VAT thickness).

Figure 2. Association between fetal adiposity (cord plasma leptin) and maternal trimester 2 lipoprotein lipase mass. Univariate correlation (Pearson's) between maternal trimester 2 lipoprotein lipase mass and fetal adiposity r=-0.69 *P*=0 .001 (n=2 data missing).

Figure 3. Proposed pathway for the contribution of maternal BMI, SAT and VAT to fetal birth weight and adiposity. In low BMI pregnant women subcutaneous adipose tissue (SAT) contains insulin sensitive (IS), hyperplasic adipocytes secreting large amounts of lipoprotein lipase (LPL) that are capable of expanding to store excess fatty acids (NEFA). In an insulin sensitive environment, this facilitates regulation of maternal glucose and triglyceride concentrations providing sufficient fuels for placental transport to support healthy fetal growth. In high BMI pregnant women, SAT contains insulin resistant (IR), hypertrophic adipocytes resulting from limited expansion of pre-adipocytes to form mature adipocytes. SAT has a reduced ability to store fatty acid which spill over and are directed to the liver increasing plasma triglyceride (TG) concentrations and are stored ectopically in visceral adipose tissue (VAT). The increasingly insulin resistance environment also raises plasma glucose levels thus increasing the supply of both fuels across a larger placenta resulting in a larger and fatter fetus.

Table 1. Maternal antenatal booking characteristics. Values are mean and standard deviation (SD) for continuous variables or number (%) for categorical variables. †n=1 missing data.

	Baseline data n=53	Longitudinal data n=45	Cord blood data n=23
Booking visit			
Age (years)	28.3 (5.1)	28.6 (5.0)	28.9 (4.6)
Smokers (number (%))	19 (35.8)	16 (35.6)	8 (34.8)
Deprivation Index			
DEPCAT Score (number (%))			
Affluent (1-2)	5 (9.4)	5 (11.1)	4 (17.4)
Intermediate (3-5)	18 (34.0)	16 (35.6)	8 (34.8)
Deprived (6-7)	30 (56.6)	24 (53.3)	11 (47.8)
Primiparous	25 (47.2)	21 (46.7)	12 (52.2)
Systolic Blood Pressure (mmHg)	118 (13)	119 (11)	118 (12)
Diastolic Blood Pressure (mmHg)	68 (9)	69 (9)	68 (9)
BMI (kg/m^2)	28.4 (6.0)	28.1 (5.7)	26.6 (5.7)
BMI range (kg/m^2)	18.0 – 46.3	18.0 – 46.3	19.0 – 46.3
Waist circumference (cm)	89.5 (14.8)	89.5 (14.8)	84.3 (11.4)
Hip circumference (cm) †	107 (15)	108 (15)	104 (15)
Waist/Hip ratio	0.83 (0.08)	0.84 (0.08)	0.81 (0.07)
Visceral fat thickness (mm)	13.4 (5.6)	13.2 (5.5)	12.1 (5.8)
Subcutaneous fat thickness (mm)	25.1 (11.4)	24.5 (10.9)	22.9 (11.0)
Visceral/Subcutaneous fat thickness	0.58 (0.23)	0.58 (0.24)	0.58 (0.27)
Visceral plus subcutaneous fat thickness (mm)	38.4 (15.7)	37.7 (15.1)	35.0 (15.2)
At delivery			
Gestation at delivery (days)	279 (9)	281 (7)	278 (8)
Fetal sex, number (%) male	29 (55)	24 (53)	15 (65)
Placental weight (g)	763 (175)	785 (175)	788 (193)
Birth weight (g)	3606 (555)	3680 (560)	3675 (628)
Birth Weight Centile	61 (31)	62 (31)	58.8 (34)
Mode of delivery (number %)			

Assisted	10 (18.9)	9 (20.0)	4 (17.4)
Elective Caesarean section	4 (7.5)	3 (6.7)	2 (8.7)
Emergency Caesarean section	7 (13.2)	6 (13.3)	3 (13.0)
Vaginal	32 (60.4)	27 (60.0)	14 (60.9)

Table 2 Maternal BMI, VAT thickness, SAT thickness and hip circumference association with fetal cord plasma markers of glucose and lipid metabolism

Mean (standard deviation) cord plasma levels (n=23) of each parameter are shown below along with their univariate association (Pearson's correlation) with maternal BMI, VAT and SAT thickness and hip circumference. The relationship between maternal BMI, VAT and SAT thickness and fetal cord plasma metabolic measures was determined by entering BMI, SAT, VAT and hip circumference in a stepwise regression model *P* to enter and *P* to stay 0.15. Mode of delivery (MOD) [assisted (A), elective Caesarean section (L), emergency Caesarean section (M) and vaginal (V) delivery] was added to the models as a confounding variable. NEFA = non-esterified fatty acid. r^2 adjusted and *P* values are stated. *analysis carried out on log-transformed data. † *P*<0.05, ‡ no terms were at *P*<0.15 to be entered into the model.

Response	Cord plasma mean (SD)	Obesity measure	Univariate correlation	Coefficient	Contribution to variance, multivariable	*P*	Contribution to variance, multivariable including MOD	*P*
Glucose (mmol/L)	4.30 (1.07)	BMI	-0.17	-0.0655	VAT 6.9%	0.013	No model‡	-
		SAT	-0.07					
		VAT	-0.34					
		Hip	0.08					
Insulin* (mU/L)	6.56 (6.64)	BMI	-0.36	-0.0332	BMI 15.4%	0.040	BMI 15.4%	0.040
		SAT	-0.37					
		VAT	-0.37					
		Hip	-0.36					
HOMA-IR*	1.29 (1.21)	BMI	-0.38	-0.0596	BMI 20.5%	0.023	BMI 20.5%	0.023

Response	Cord plasma mean (SD)	Obesity measure	Univariate correlation	Coefficient	Contribution to variance, multivariable	*P*	Contribution to variance, multivariable including MOD	*P*
		SAT	-0.35					
		VAT	-0.45†					
		Hip	-0.28					
Triglyceride (mmol/L)*	0.72 (0.65)	BMI	0.16	0.01994	VAT 14.8%	0.043	VAT 9.3%	0.047
		SAT	0.30					
		VAT	0.42†					
		Hip	0.14					
NEFA* (mmol/L)	0.19 (0.12)	BMI	0.26	0.0236	VAT 17.5%	0.034	VAT 12.8%	0.075
		SAT	0.26					
		VAT	0.47†					
		Hip	0.28					
Total cholesterol* (mmol/L)	1.79 (0.65)	BMI	0.33	0.00938	VAT 14.0%	0.049	Hip 16.8%	0.002
		SAT	0.42†					
		VAT	0.43†					
		Hip	0.33					
HDL cholesterol (mmol/L)	0.74 (0.18)	BMI	0.12		No model‡		-	-
		SAT	0.02					
		VAT	-0.11					
		Hip	0.15					

Table 3 Maternal BMI, abdominal visceral and subcutaneous adipose tissue and hip circumference associations with maternal markers of gestational fuel exposure Mean (standard deviation) maternal plasma trimester 2 levels or AUC trimester 1 to trimester 3 (n=45) are shown below along with their univariate association (Pearson's correlation) with maternal BMI, VAT and SAT thickness and hip circumference.

The relationship between maternal BMI, visceral adipose tissue (VAT) and upper body subcutaneous adipose tissue (SAT) thickness and maternal plasma metabolic measures was determined by entering BMI, SAT, VAT and hip circumference in a stepwise regression model *P* to enter and *P* to stay 0.15. r^2 adjusted and *P* values are stated. *analysis carried out on log-transformed data. † *P*<0.05, ‡ no terms were at *P*<0.15 to be entered into the model.

Response	Maternal plasma mean (SD)	Obesity measure	Univariate correlation	Coefficient	Contribution to variance, multivariable	*P*
Maternal T2 Glucose (mmol/L)*	5.41 (1.17)	BMI	0.38†	0.00591	BMI 12.5%	0.011
		SAT	0.20			
		VAT	0.32†			
		Hip	0.28			
Maternal T2 Triglyceride (mmol/L)*	2.41 (0.73)	BMI	0.20	0.00348	SAT 5.1%	0.078
		SAT	0.27			
		VAT	0.17			
		Hip	0.12			
Maternal T2 HOMA*	12.3 (10.8)	BMI	0.41†	0.0313	BMI 15.1%	0.005
		SAT	0.31†			
		VAT	0.37†			
		Hip	0.33†			
Maternal AUC glucose (mmol/l x weeks)*	120 (26)	BMI	0.39†	0.00563	BMI 15.3%	0.009
		SAT	0.17			
		VAT	0.27			
		Hip	0.34†			
Maternal AUC triglyceride (mmol/L x weeks)	50 (14)	BMI	0.18		No model‡	
		SAT	0.27			
		VAT	0.06			
		Hip	0.15			
Maternal AUC HOMA (HOMAx	240 (186)	BMI	0.35†	0.02074	BMI 10.0%	0.021
		SAT	0.25			
		VAT	0.24			

Response	Maternal plasma mean (SD)	Obesity measure	Univariate correlation	Coefficient	Contribution to variance, multivariable	*P*
weeks)*		Hip	0.31†			

Figure 1

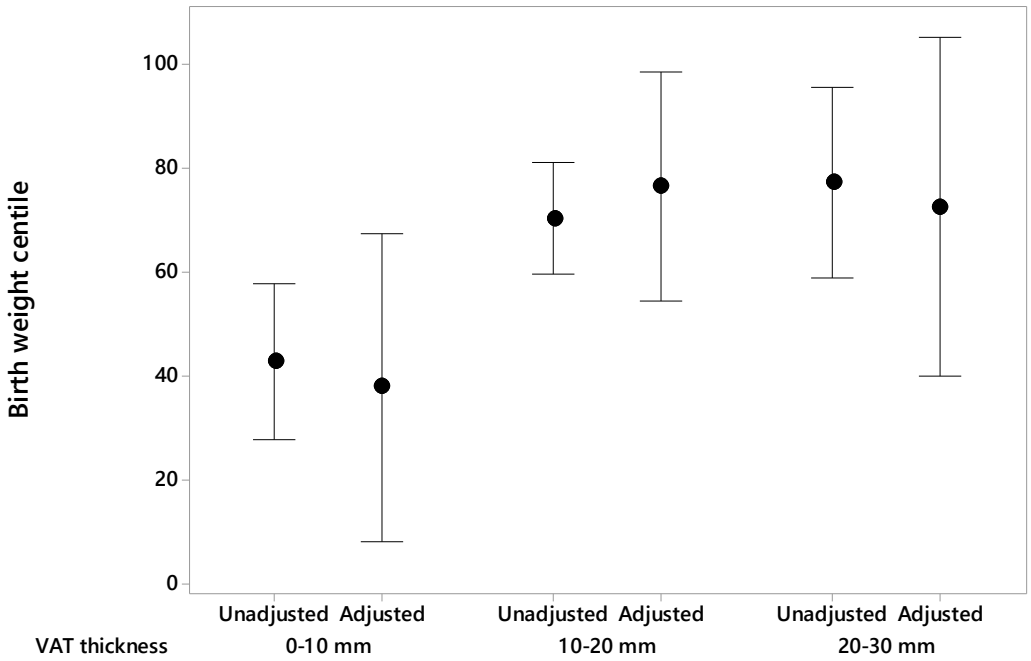

Birth weight centile
100
80
60
40
20
0
Unadjusted
Adjusted
Unadjusted
Adjusted
Unadjusted
Adjusted
VAT thickness
0-10 mm
10-20 mm
20-30 mm

Figure 2.

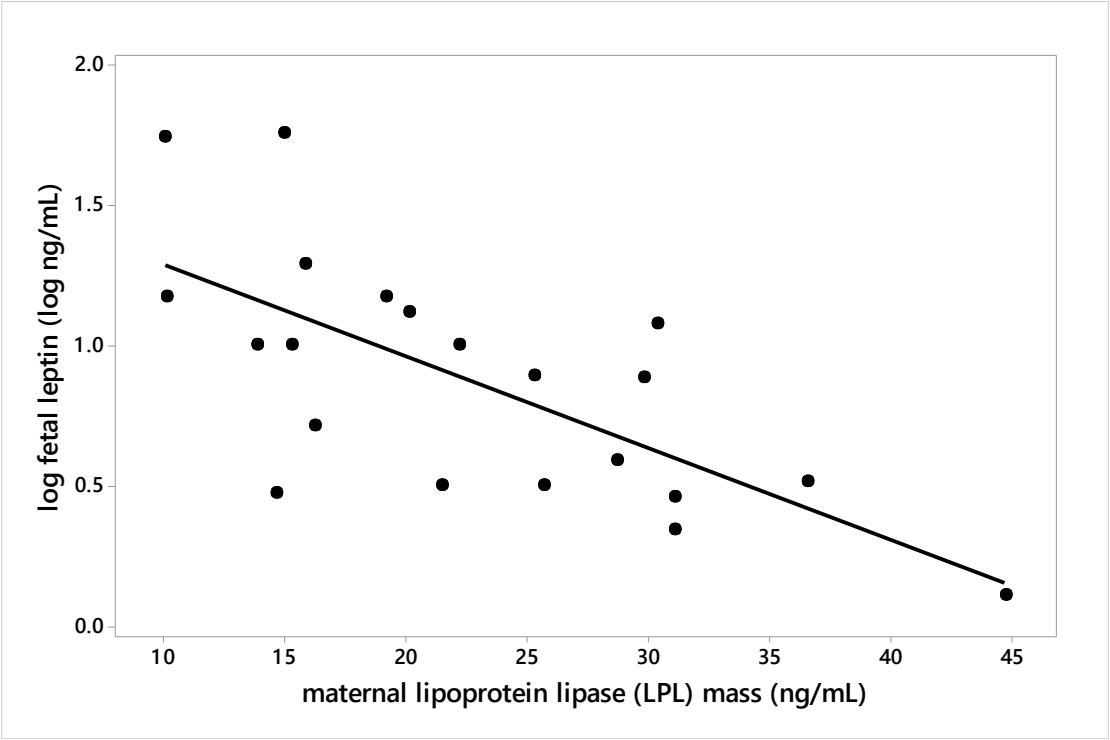
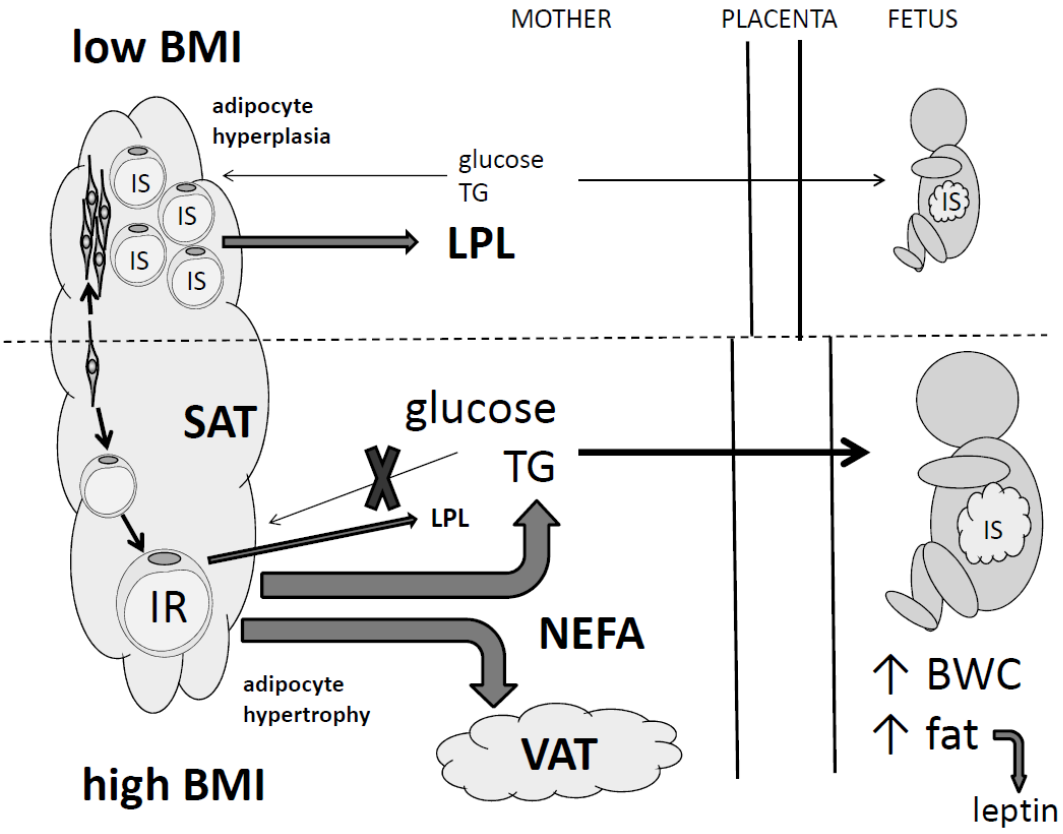

log fetal leptin (log ng/mL)
2.0
1.5
1.0
0.5
0.0
10
15
20
25
30
35
40
45
maternal lipoprotein lipase (LPL) mass (ng/mL)

Figure 3


MOTHER
PLACENTA
FETUS
low BMI
adipocyte
hyperplasia
glucose
TG
LPL
IS
IS
IS
IS
IS
SAT
glucose
TG
LPL
IR
NEFA
adipocyte
hypertrophy
VAT
high BMI
IS
↑ BWC
↑ fat
leptin