

**The impact of maternal glycemia and obesity on early postnatal growth
in a non-diabetic Caucasian population.**

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Abstract

Objective. Offspring of mothers with diabetes have increased birthweight and higher rates of obesity in early childhood. The relative role of maternal glycaemia and maternal obesity is uncertain. We therefore studied the impact of maternal glycaemia and maternal obesity on offspring birth measures, and early postnatal growth in non diabetic pregnancies.

Research Design and Methods. We studied 547 full term, singleton babies of non-diabetic parents. Data available included: parental height and weight, maternal pre-pregnant weight, maternal fasting plasma glucose (FPG) at 28 weeks gestation, offspring weight and length, at birth, 12 weeks, 1 year and 2 years of age. Relationships between parental and offspring measures were estimated using Pearson correlations.

Results. Maternal FPG was correlated with offspring birthweight ($r=0.25$, $p<0.001$), length ($r=0.17$, $p<0.001$), and BMI ($r=0.2$, $p<0.001$) but was not correlated with offspring growth at 12 weeks. Maternal pre-pregnancy BMI was significantly correlated with offspring weight ($r=0.26$, $p<0.001$), length ($r=0.12$, $p=0.01$) and BMI at birth ($r=0.26$, $p<0.001$), and remained correlated with offspring weight ($r=0.13-0.14$, $p=0.007-0.002$) and BMI ($r=0.14-0.19$ $p=0.002-<0.001$) during the first two years. Paternal BMI was correlated with offspring weight from 12 weeks onwards ($r=0.11-0.22$, $p=0.017-<0.001$), length ($r=0.10-0.12$, $p=0.01-0.05$) and BMI from 1 year ($r=0.16-0.25$, $p=<0.001$).

Conclusion. In a non diabetic cohort, the effect of maternal glycaemia on birthweight is transitory, while the impact on growth of maternal BMI continues into early childhood. The independent association of paternal BMI with offspring postnatal growth suggests the impact of parental BMI could be explained by genetic factors, shared environment or both.

Introduction

There is strong evidence that the offspring of mothers with pre-pregnancy Type 2 and gestational diabetes not only have increased birthweight(1-3), but show increased obesity in childhood and early adult life (2-10). These mothers have an increased BMI as well as being hyperglycemic (11-13). Both of these might contribute to obesity in the offspring in early life(14). Possible mechanisms to explain the relative obesity in early childhood of the offspring include programming by the maternal intra-uterine environment, inheriting a genetic predisposition to obesity, or, maternal and childhood obesity representing a shared familial environment.

Insulin mediated growth of the fetus reflects maternal glycaemia, with birthweight being increased in diabetic pregnancies, and correlated with maternal glycaemia, both fasting and stimulated levels, in the non-diabetic pregnancy (15-18). The impact of glycaemia within the normal range on early postnatal growth in European Caucasians is uncertain.

By studying the effect of maternal glycaemia on early postnatal growth in the non diabetic population it may give insights into the mechanisms of the effects seen in the offspring of diabetic mothers. We therefore aimed to study the impact of maternal glycaemia in the non diabetic pregnancy, and parental BMI on birth measures and early postnatal growth of offspring.

Research Design and Methods.

We studied 547 full term (gestation >37 weeks), singleton babies and their parents from the Exeter Family Study of Childhood Health (EFSOCH). Subjects with diabetes were excluded and all mothers had a fasting glucose <5.5 mmol/l (100mg/dl) at 28 weeks

gestation. EFSOCH was set up to study fetal and early postnatal growth, by investigating the role of genes and genetic factors within a normal Caucasian population. This is an ongoing, prospective, community based study, within a specific area of central Exeter, as defined by postcode. The study protocol has been described in detail previously(19). Ethical approval was given by the North and East Devon local ethics committee.

Data collected:

Height (to nearest 0.1cm using the Harpenden stadiometer), and weight(to nearest 0.1kg using Tanita electric scales) were measured on both parents at 28 weeks of gestation. All measures were taken prospectively, by specially trained research midwives. Inter rater coefficient of variation (CV) between the research midwives for parental weight and height was <1%. Mother's pre-pregnant weight was self reported.

Measurements taken on the offspring at birth, 12 weeks, 1 year and 2 years include: length (to nearest 0.1cm using the Harpenden stadiometer) and weight (to nearest 0.1kgs, using Soehnle scales). Limits of agreement (mean +/- 2SD) between the research midwives were within +/- 1cm for all neonatal measures. We used BMI (wt / ht^2) at birth rather than ponderal index to give consistency with postnatal measures.

Fasting plasma glucose was obtained on all mothers at 28 weeks gestation, and the assay was carried out by the pathology laboratories at the Royal Devon & Exeter Hospital, Exeter (UK).We assigned Socio-economic status (SES) by Townsend Scores based on Enumeration districts by postcode(20).

Gestation was calculated from last menstrual period (LMP) in women who had regular periods and were confident of the date of their

last period (n=338). Where there was doubt about the LMP, gestation was calculated by the "dating scan" (n=209) done early in pregnancy (12.6 +/- 1.6 weeks)

Statistics:

Data were summarized as means and standard deviations. Standard deviation scores (SDS) were calculated for weight, length and BMI on all babies at birth, 12 weeks, 1 year and 2 years of age. Relationships between maternal glycaemia, maternal pre-pregnant BMI, paternal BMI and child growth measures were estimated using partial correlations (Pearson), in all cases adjusting for sex, gestational age, parity, maternal smoking and SES. Corrections were made for corresponding parental size to adjust for the effects of assortative mating. Multiple linear regression used Standard Deviation Scores (SDS) to enable comparison both between variables, and across time points.

Maternal fasting plasma glucose (FPG), maternal pre-pregnancy BMI and paternal BMI tertiles were produced. Analysis of variance (ANOVA) was used to assess significant differences between the tertiles and child growth measures at each time point.

Results:

Characteristics of the study population: Mothers were on average 30 years old, with a mean 28-week FPG of 4.3 mmol/l and a mean BMI of 27.8. 219 (40%) were primiparous, and 69 (12%) smoked. The fathers were on average 33 years old, with a mean BMI of 26.8. The babies (297males, 250 females) were born at a mean of 40.2 weeks gestation, weighed 3.5 kgs, and were 50.3cms long. The median Townsend score for families in EFSOCH was -0.30 (range -6.62 to 8.85). Full data from birth to 2 years was available on 427 babies. There was no difference between those with full follow up measures and those without in terms of birth: weight (3563g v 3485g, p=0.12), length (50.3cm v

50.0cm, p=0.13), gestation (40.2 v 40.1 wks, p=0.54) and maternal BMI (24.0 v 23.5, p=0.37), but those with full follow up had lower deprivation scores (-0.47 v 0.58, p=0.005).

(a) Correlations of birth and early childhood anthropometry with maternal glycaemia. (Table 1)

Maternal FPG was significantly correlated with child birthweight when corrected for the common confounders of sex, gestation, parity, smoking, and SES (r=0.25, p<0.001). This remained significant when corrected for maternal pre-pregnant BMI (r=0.19, p<0.001). There was no correlation with weight from 12 weeks to 2 years of age. Maternal glucose was significantly correlated with offspring birth length (r=0.17, p<0.001), but not at the later time points. Maternal FPG was correlated with offspring birth BMI (r=0.2, p<0.001) and also ponderal index (r=0.13 p=0.004) but not with BMI after birth. (table 2). These relationships are shown graphically by subdividing the offspring into tertiles defined by maternal glycaemia (figure 1).

(b) Correlations of birth and early childhood anthropometry with maternal pre-pregnancy BMI. (Table 1)

Maternal pre-pregnancy BMI was significantly correlated with child weight at birth (r=0.26, p<0.001), when corrected for common confounders of sex, gestation, parity, smoking, and SES. This remained following correction for maternal glycaemia (r=0.19, p<0.001), and paternal BMI (r=0.19, p<0.001). In contrast to maternal glucose, the maternal pre-pregnancy BMI remained correlated with early childhood weight (r=0.13-0.14, p=0.007-0.002). Maternal BMI and offspring BMI were significantly correlated from birth into early childhood (r=0.26-0.19, p<0.001-p=0.002). These relationships are show graphically by

subdividing the offspring into tertiles defined by maternal pre-pregnancy BMI (figure 2)

(c) Correlations of birth and early childhood anthropometry with paternal BMI. (Table 1)

Associations between maternal BMI and offspring postnatal BMI could represent a response to the intra-uterine environment, a shared external environment or a genetic predisposition. To examine these possibilities we looked at associations with paternal BMI which could not directly alter the intra-uterine environment. Paternal BMI was not correlated with offspring weight, length or BMI at birth, but was correlated with offspring weight from 12 weeks ($r=0.11-0.22$, $p=0.017- <0.001$), offspring length and offspring BMI from 1 year ($r=0.10-0.25$, $p=0.05-p<0.001$). These relationships are shown graphically by subdividing the offspring into tertiles defined by paternal BMI (figure 3).

(d) Correlations of paternal, maternal, and offspring BMI.

We assessed whether the correlations between parental BMI, and offspring BMI at ages 1 and 2 were likely to be independent. Paternal BMI was correlated with maternal pre-pregnancy BMI ($r=0.13$, $p=0.004$). Maternal BMI was correlated with offspring BMI at 1 year ($r=0.19$, $p<0.001$) and 2 years of age ($r=0.18$, $p<0.001$). These remained correlated after correction for paternal BMI (1yr: $r=0.18$, $p=<0.001$, 2yrs: $r=0.14$, $p=0.004$). Similarly paternal BMI was correlated with offspring BMI at both time points, (1yr: $r=0.16$, $p<0.001$ and 2yrs: $r=0.23$, $p<0.001$). These remained correlated after correction for maternal BMI (1yr: $r=0.13$, $p=0.009$, and 2yrs: $r=0.21$, $p<0.001$). These results suggest that maternal and paternal BMI both have an independent but additive effect on offspring BMI.

(e) Multiple linear regression analysis (MLRA)

MLRA was used to assess the relative strength of MFG, maternal pre-pregnancy BMI and paternal BMI and measures of offspring growth. (Table 2). MFG (SDS) was the strongest determinant of offspring birthweight ($B=0.510$, $p<0.001$). By 2 years paternal BMI (SDS) showed the strongest association ($B=0.225$, $p<0.001$).

Discussion

Our study of normoglycaemic mothers showed an impact of maternal glycaemia on fetal growth, but this did not persist postnatally. In keeping with other studies (15-18), we demonstrated maternal glycaemia within the normal range was correlated with parameters of fetal growth at birth: weight, length and BMI. This effect is most pronounced in the mothers in the upper tertile of glycemic values, suggesting the macrosomia seen in pregnancies complicated by type 2, or gestational, diabetes may be a continuum of the effect of “normal” glucose on birthweight in the non-diabetic pregnancy. We have demonstrated that in the normoglycaemic population, the impact of glycaemia on offspring growth is transient as it is not detectable at 12 weeks of age. This is in keeping with findings that despite improvements in the glycaemic management of diabetic pregnancies in recent years, there has been no decrease in the risk of obesity in the offspring of mothers with diabetes (21), and in a cohort of mothers with well controlled gestational diabetes their fasting glycaemia was not a major determinant of childhood obesity(22).

Maternal pre-pregnancy BMI was significantly correlated with birthweight ($r=0.25$ $p<0.001$). This remained significant after correcting for maternal glucose ($r=0.19$, $p<0.001$) and was clearest in the mothers in the higher BMI tertile. The increase in

offspring weight with maternal BMI persisted in the first two years of life and reflected an increase in BMI and not height. This suggests that the persisting increase in obesity seen in the offspring of gestational or type 2 diabetic pregnancies may be attributable more to increased maternal obesity rather than maternal glycaemia. This supports the work of Simmonds (23), who hypothesized that fuel mediated teratogenesis may be driven by maternal obesity, and is consistent with studies suggesting that when dietary treatment aimed at reducing weight gain in mothers with gestational diabetes is instituted, there is a subsequent reduction in birthweight of the offspring(24), and that offspring obesity is not increased when controlling for paternal obesity (25). Furthermore, in a population of low income families, the risk of offspring obesity doubles between the ages of 2-4 where the mother is obese in early pregnancy(26).

Maternal BMI had no association with birth length, while the association with child weight persists, suggesting that the effect of maternal BMI may be greater on the “fat” component of child weight, than on the skeletal component. This is in keeping with previous work suggesting offspring of mothers with gestational diabetes have increased body fat, independent of birthweight (27).

In contrast to the maternal effects, paternal BMI has no effect on offspring birthweight, but is associated with offspring weight and BMI with increasing age, i.e. the further away from the maternal environment. Previous studies have suggested that paternal BMI becomes a significant predictor of offspring weight, after 4 years of age (28-30). However, in our study the association between paternal BMI and offspring weight as seen from 12 weeks, is similar or possibly greater than the association of maternal pre-pregnancy BMI. This is in contrast to two studies suggesting

parental anthropometry and child anthropometry were not related in the first two years of life (28, 31). However, both these studies had small sample sizes, and one only studied “high” and “low” maternal BMI and not a continuum(31). Our study is in agreement with others which identify parental obesity as risk factors for offspring obesity (32, 33) and metabolic syndrome,(8) of which obesity is a feature. The impact of maternal and paternal BMI on postnatal weight and BMI are independent and additive. These parental influences may reflect a shared environment, as there is an association between maternal and paternal BMI although the association with offspring BMI is stronger. This would suggest that as early as one year, parental attitudes to food impact more strongly on their offspring’s food consumption than each others. An alternative explanation of the associations between the BMI of each parent and their offspring is that it could also indicate a genetic effect. It is known that obesity has a genetic component although the major genetic determinants are not known at a molecular level (34, 35). Our study is not able to differentiate whether the observed paternal association reflects a shared environment, a genetic effect or, as is most likely, a combination of environment and genes.

Conclusion: We have demonstrated that the impact of maternal glycaemia on birthweight, seen in our non diabetic cohort is transient, in contrast to the association of maternal BMI on offspring weight and BMI which continues into early childhood. The association between paternal BMI and early childhood growth after 12 weeks suggests that the persisting impact of maternal BMI may be mediated through either a shared environment or genetic influences.

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Table 1. Partial correlations of offspring weight, length, and body mass index (BMI) at: birth, 12 weeks, 1 year, and 2 years of age, with maternal fasting glucose, maternal pre-pregnancy BMI and Paternal BMI, corrected for common confounders (sex, gestation, parity, smoking, and socioeconomic status).

	Weight		Length		BMI	
Maternal fasting glucose	r	p	r	p	r	p
Birth	0.25	<0.001	0.17	<0.001	0.2	<0.001
12 weeks	0.37	0.40	0.05	0.31	0.02	0.74
1 year	-0.04	0.41	0.01	0.79	-.06	.19
2 years	0.03	0.57	0	0.96	.03	0.53
Maternal pre-pregnancy BMI						
Birth	0.26	<0.001	0.12	0.01	0.26	<0.001
12 weeks	0.14	0.002	0.04	0.35	0.14	0.002
1 year	0.13	0.007	-0.04	0.45	0.19	<0.001
2 year	0.14	0.004	0.01	0.91	0.17	<0.001
Paternal BMI						
Birth	0.06	0.15	0.05	0.27	0.04	0.33
12 weeks	0.11	0.017	0.07	0.11	0.08	0.07
1 year	0.20	<0.001	0.12	0.01	0.16	<0.001
2 years	0.22	<0.001	0.10	0.05	0.25	<0.001

Table 2.

Regression analysis with offspring weight Standard Deviation Score (SDS) at four time points as the response variables, and Maternal Fasting Plasma Glucose (Mat FPG), Maternal pre-pregnancy Body Mass Index SDS (Mat pp BMI SDS), and Paternal Body Mass Index SDS (Pat BMI SDS) as the explanatory variables.

variables	Birthweight SDS				12 week weight SDS			
	B	SE	t	p	B	SE	t	p
Mat FPG SDS	.510	.118	4.31	<0.001	-.038	.048	-.78	.435
Mat pp BMI SDS	.038	.009	4.31	<0.001	.122	.048	2.55	.011
Pat BMI SDS	.003	0.10	0.31	0.774	.075	.045	1.64	.101
	1 year weight SDS				2 year weight SDS			
	B	SE	t	p	B	SE	t	p
Mat FPG SDS	-.10	.050	-2.0	.044	-.055	.051	-1.07	.283
Mat pp BMI SDS	.121	.050	2.41	.016	.110	.053	2.09	.037
Pat BMI SDS	.182	.048	3.81	<0.001	.225	.050	4.52	<0.001

Variables also in model but not shown

are: fetal sex, maternal smoking, parity, and Socio Economic Status (SES)

Figure 1.

Offspring weight, length, and Body Mass Index (BMI), in the first 2 years of life, shown according to tertiles of maternal fasting glucose, measured at 28 weeks gestation.

Data shown as mean standard deviation score (SDS), corrected for sex and gestation (birth only), with 95% confidence interval (CI). Differences between tertiles were assessed at each time point using analysis of variance, ** = $p < 0.01$, *** = $p < 0.001$.

Solid line represents upper tertile, dotted line represents middle tertile, and dashed line represents lower tertile.

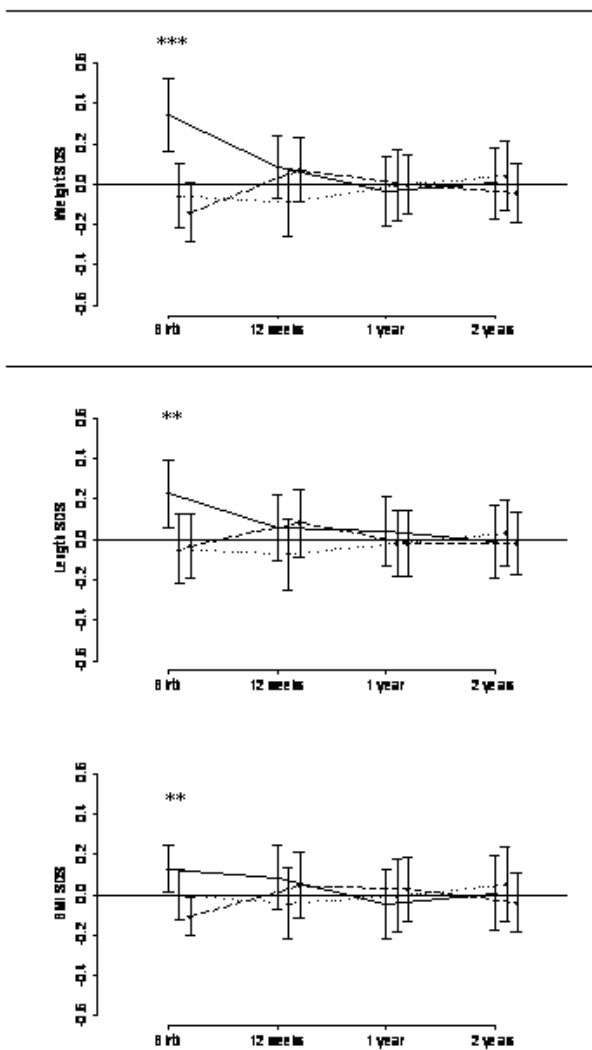


Figure 2.

Offspring weight, length, and BMI in the first 2 years of life, shown according to tertiles of maternal pre-pregnancy BMI

Data shown as mean standard deviation score (SDS), corrected for sex and gestation (birth only), with 95% confidence interval (CI).

Differences between tertiles were assessed at each time point using analysis of variance,

* = $p < 0.5$, ** = $p < 0.01$, *** = $p < 0.001$.

Solid line represents upper tertile, dotted line represents middle tertile, and dashed line represents lower tertile.

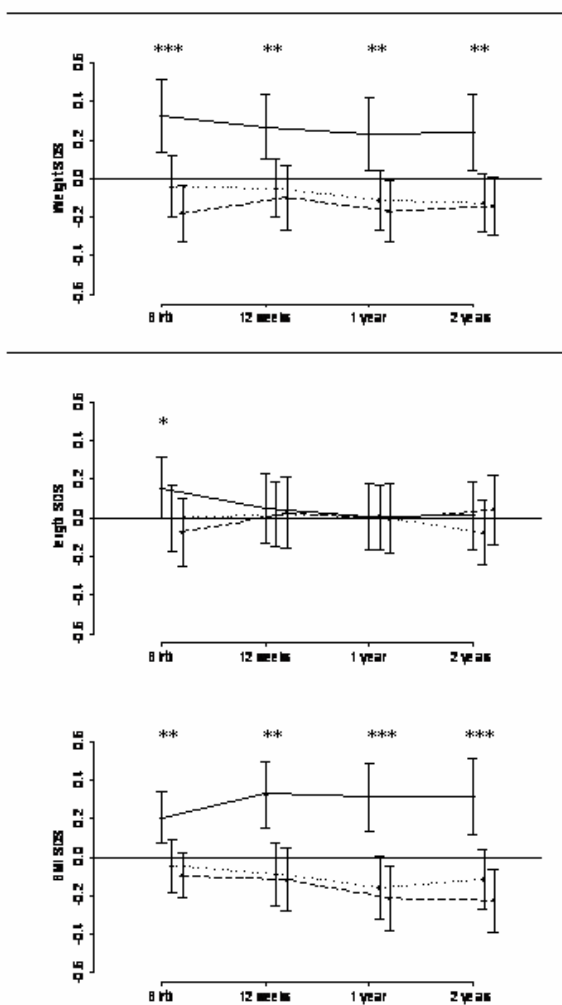


Figure 3.

Offspring weight, length, and BMI in the first 2 years of life, shown according to tertiles of paternal BMI.

Data shown as mean standard deviation score (SDS), corrected for sex and gestation (birth only), with 95% confidence interval (CI).

Differences between tertiles were assessed at each time point using analysis of variance, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Solid line represents upper tertile, dotted line represents middle tertile, and dashed line represents lower tertile.

