The Impact of Maternal Glycemia and Obesity on Early Postnatal Growth in a Nondiabetic Caucasian Population

BRIDGET KNIGHT, PHD[1,2]
BEVERLEY M. SHIELDS, PHD[1]
ANITA HILL[1]
ROY J. POWELL, PHD[3]
DAVID WRIGHT, PHD[4]
ANDREW T. HATTERSLEY, DM[1]

OBJECTIVE — Offspring of mothers with diabetes have increased birth weight and higher rates of obesity in early childhood. The relative role of maternal glycemia and maternal obesity is uncertain. We therefore studied the impact of maternal glycemia and maternal obesity on offspring birth measures and early postnatal growth in nondiabetic pregnancies.

RESEARCH DESIGN AND METHODS — We studied 547 full-term singleton babies of nondiabetic parents. Data available included parental height and weight; maternal prepregnant weight; maternal fasting plasma glucose (FPG) at 28 weeks of gestation; and offspring weight and length at birth, 12 weeks of age, and 1 and 2 years of age. Relationships between parental and offspring measures were estimated using Pearson correlations.

RESULTS — Maternal FPG was correlated with offspring birth weight ($r = 0.25$, $P < 0.001$), 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 prepregnancy 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 ($r = 0.14–0.19$, $P = 0.002$ to <0.001) during the first 2 years. Paternal BMI was correlated with offspring weight from 12 weeks onwards ($r = 0.11–0.22$, $P = 0.017$ to <0.001), length ($r = 0.10–0.12$, $P = 0.01–0.05$), and BMI from 1 year onwards ($r = 0.16–0.25$, $P = <0.001$).

CONCLUSIONS — In a nondiabetic cohort, the effect of maternal glycemia on birth weight 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 that the impact of parental BMI could be explained by genetic factors, shared environment, or both.

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There is strong evidence that the offspring of mothers with prepregnancy type 2 and gestational diabetes not only have increased birth weight (1–3), but also show increased obesity in childhood and early adult life (2–10). These mothers have an increased BMI and are also hyperglycemic (11–13), both of which may 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 intrauterine 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 glycemia, with birth weight being increased in diabetic pregnancies, and correlates with maternal glycemia, in both fasting and stimulated levels, in the nondiabetic pregnancy (15–18). The impact of glycemia within the normal range on early postnatal growth in European Caucasians is uncertain.

Studying the effect of maternal glycemia on early postnatal growth in the nondiabetic population may give insight into the mechanisms of the effects seen in the offspring of diabetic mothers. We therefore aimed to study the impact of maternal glycemia in the nondiabetic 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 (100 mg/dl) at 28 weeks of 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).

Ethics approval was given by the North and East Devon local ethics committee.

Data collected

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

Measurements taken on the offspring at birth, 12 weeks of age, and 1 and 2 years of age include length (to nearest 0.1 cm using

From [1]Peninsula Medical School, Exeter, U.K.; the [2]Maternity Unit, Heavitree Hospital, Royal Devon and Exeter NHS Trust, Exeter, U.K; the [3]Research and Development Support Unit, Exeter, U.K.; and the [4]School of Mathematics and Statistics, University of Plymouth, Plymouth, U.K.

Address correspondence and reprint requests to Professor Andrew T. Hattersley, Diabetes Research, Peninsula Medical School, Barrack Road, Exeter, EX2 5AX, U.K. Email: andrew.hattersley@pms.ac.uk.

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Abbreviations: EFSOCH, Exeter Family Study of Childhood Health; FPG, fasting plasma glucose; SDS, SD scores; SES, socio-economic status.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Partial correlations of offspring weight, length, and BMI at birth, 12 weeks of age, and 1 and 2 years of age with maternal fasting glucose, maternal prepregnancy BMI, and paternal BMI, corrected for common confounders (sex, gestation, parity, smoking, and socioeconomic status)*

	Weight		Length		BMI	
	r	*P*	*r*	*P*	*r*	*P*
Maternal fasting glucose						
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	−0.06	0.19
2 years	0.03	0.57	0	0.96	0.03	0.53
Maternal prepregnancy 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 years	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

the Harpenden stadiometer) and weight (to nearest 0.1 kg using Soehnle scales). Limits of agreement (mean ± 2 SD) between the research midwives were within ± 1 cm for all neonatal measures. We used BMI (kg/m^2) at birth rather than ponderal index to give consistency with postnatal measures.

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

Gestation was calculated from last menstrual period in women who had regular periods and were confident of the date of their last period (n = 338). Where there was doubt about the last menstrual period, gestation was calculated by the "dating scan" (n = 209) done early in pregnancy (12.6 ± 1.6 weeks)

Statistics

Data were summarized as mean ± SD. SD scores (SDS) were calculated for weight, length, and BMI on all babies at birth, 12 weeks of age, and 1 and 2 years of age. Relationships between maternal glycemia, maternal prepregnant 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 SDS to enable comparison both between variables and across time points.

Maternal FPG, maternal prepregnancy BMI, and paternal BMI tertiles were produced. ANOVA was used to assess significant differences between the tertiles and child growth measures at each time point.

Table 2—*Regression analysis with offspring weight SDS at four time points as the response variables, and maternal FPG, maternal prepregnancy BMI SDS, and paternal BMI SDS as the explanatory variables*

	Maternal FPG SDS	Maternal prepregnancy BMI SDS	Paternal BMI SDS
Birthweight SDS			
B	0.510	0.038	0.003
SE	0.118	0.009	0.10
t	4.31	4.31	0.31
P	<0.001	<0.001	0.774
12-week weight SDS			
B	−0.038	0.122	0.075
SE	0.048	0.048	0.045
t	−0.78	2.55	1.64
P	0.435	0.011	0.101
1-year weight SDS			
B	−0.10	0.121	0.182
SE	0.050	0.050	0.048
t	−2.0	2.41	3.81
P	0.044	0.016	<0.001
2-year weight SDS			
B	−0.055	0.110	0.225
SE	0.051	0.053	0.050
t	−1.07	2.09	4.52
P	0.283	0.037	<0.001

Variables also in model but not shown are fetal sex, maternal smoking, parity, and SES.

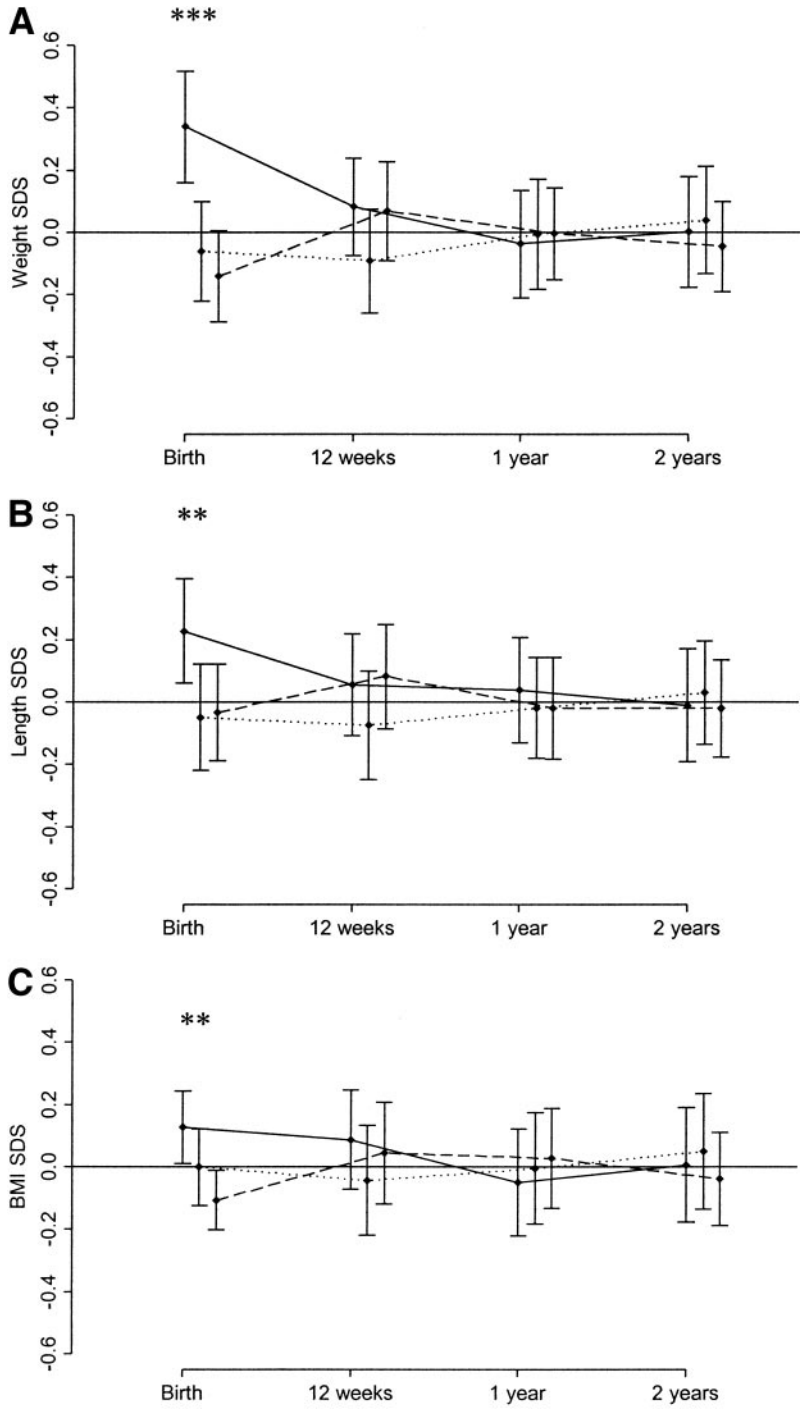

Figure 1—*Offspring weight (A), length (B), and BMI (C) in the first 2 years of life, shown according to tertiles of maternal fasting glucose, measured at 28 weeks of gestation. Data are shown as mean SDS corrected for sex and gestation (birth only), with 95% CI. Differences between tertiles were assessed at each time point using ANOVA. **P < 0.01, ***P < 0.001. Solid line represents upper tertile, dotted line represents middle tertile, and dashed line represents lower tertile.*

RESULTS

Characteristics of the study population

Mothers were on average 30 years of age, with a mean 28-week FPG of 4.3 mmol/l and a mean BMI of 27.8 kg/m^2; 219 (40%) were primiparous, and 69 (12%) smoked. The fathers were on average 33 years of age, with a mean BMI of 26.8 kg/m^2. The babies (297 males and 250 females) were born at a mean of 40.2 weeks of gestation, weighed 3.5 kg, and were 50.3 cm 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 were available on 427 babies. There was no difference between those with full follow-up measures and those without in terms of birth: weight (3,563 vs. 3,485 g, $P = 0.12$), length (50.3 vs. 50.0 cm, $P = 0.13$), gestation (40.2 vs. 40.1 weeks, $P = 0.54$), and maternal BMI (24.0 vs. 23.5 kg/m^2, $P = 0.37$). However, those with full follow-up had lower deprivation scores (−0.47 vs. 0.58, $P = 0.005$).

Correlations of birth and early childhood anthropometry with maternal glycemia

Maternal FPG was significantly correlated with child birth weight when corrected for the common confounders of sex, gestation, parity, smoking, and SES ($r = 0.25$, $P < 0.001$) (Table 1). This remained significant when corrected for maternal prepregnant 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 later time points. Maternal FPG was correlated with offspring birth BMI ($r = 0.2$, $P < 0.001$) and 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 glycemia (Fig. 1).

Correlations of birth and early childhood anthropometry with maternal prepregnancy BMI

Maternal prepregnancy 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 (Table 1). This remained following correction for maternal glycemia ($r = 0.19$, $P < 0.001$) and paternal BMI ($r = 0.19$, $P < 0.001$). In contrast to maternal glucose, the maternal prepregnancy 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 ($r = 0.26–0.19$, $P < 0.001$ to 0.002). These relationships are shown graphically by subdividing the offspring into tertiles defined by maternal prepregnancy BMI (Fig. 2)

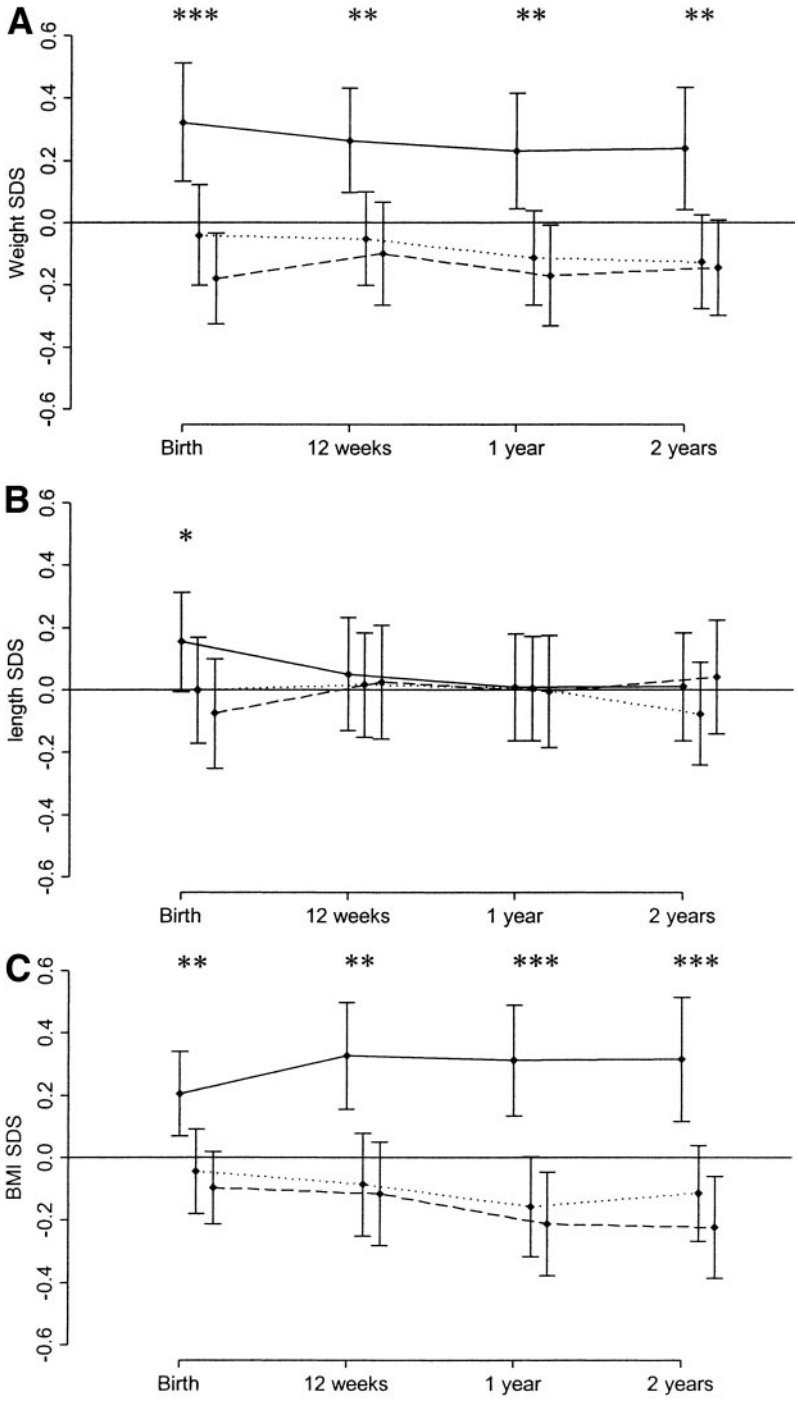

Figure 2—*Offspring weight* (A)*, length* (B)*, and BMI* (C) *in the first 2 years of life, shown according to tertiles of maternal prepregnancy BMI. Data are shown as mean SDS corrected for sex and gestation (birth only), with 95% CI. Differences between tertiles were assessed at each time point using ANOVA.* *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.*

Correlations of birth and early childhood anthropometry with paternal BMI

Associations between maternal BMI and offspring postnatal BMI could represent a response to the intrauterine environment, a shared external environment, or a genetic predisposition (Table 1). To examine these possibilities, we examined associations with paternal BMI that could not directly alter the intrauterine 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 to <0.001) and offspring length and BMI from 1 year (r = 0.10–0.25, P = 0.05 to <0.001). These relationships are shown graphically by subdividing the offspring into tertiles defined by paternal BMI (Fig. 3).

Correlations of paternal, maternal, and offspring BMI

We assessed whether the correlations between parental BMI and offspring BMI at ages 1 and 2 years were likely to be independent. Paternal BMI was correlated with maternal prepregnancy 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 (r = 0.18, $P < 0.001$) of age. These remained correlated after correction for paternal BMI (1 year r = 0.18, $P < 0.001$; 2 years r = 0.14, P = 0.004). Similarly, paternal BMI was correlated with offspring BMI at both time points (1 year r = 0.16, $P < 0.001$; 2 years r = 0.23, $P < 0.001$). These remained correlated after correction for maternal BMI (1 year r = 1.3, P = 0.009; 2 years r = 0.21, $P < 0.001$). These results suggest that maternal and paternal BMI both have an independent but additive effect on offspring BMI.

Multiple linear regression analysis

Multiple linear regression analysis was used to assess the relative strength of maternal fasting glucose, maternal prepregnancy BMI, and paternal BMI and measures of offspring growth (Table 2). Maternal fasting glucose (SDS) was the strongest determinant of offspring birth weight (B = 0.510, $P < 0.001$). By 2 years, paternal BMI (SDS) showed the strongest association (B = 0.225, $P <$ 0.001).

CONCLUSIONS — Our study of normoglycemic mothers showed an impact of maternal glycemia on fetal growth, but this did not persist postnatally. In keeping with other studies (15–18), we demonstrated maternal glycemia within the normal range was correlated with parameters of fetal growth at birth, including 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 birth weight in the nondiabetic pregnancy. We have demonstrated that in the normoglycemic popu-

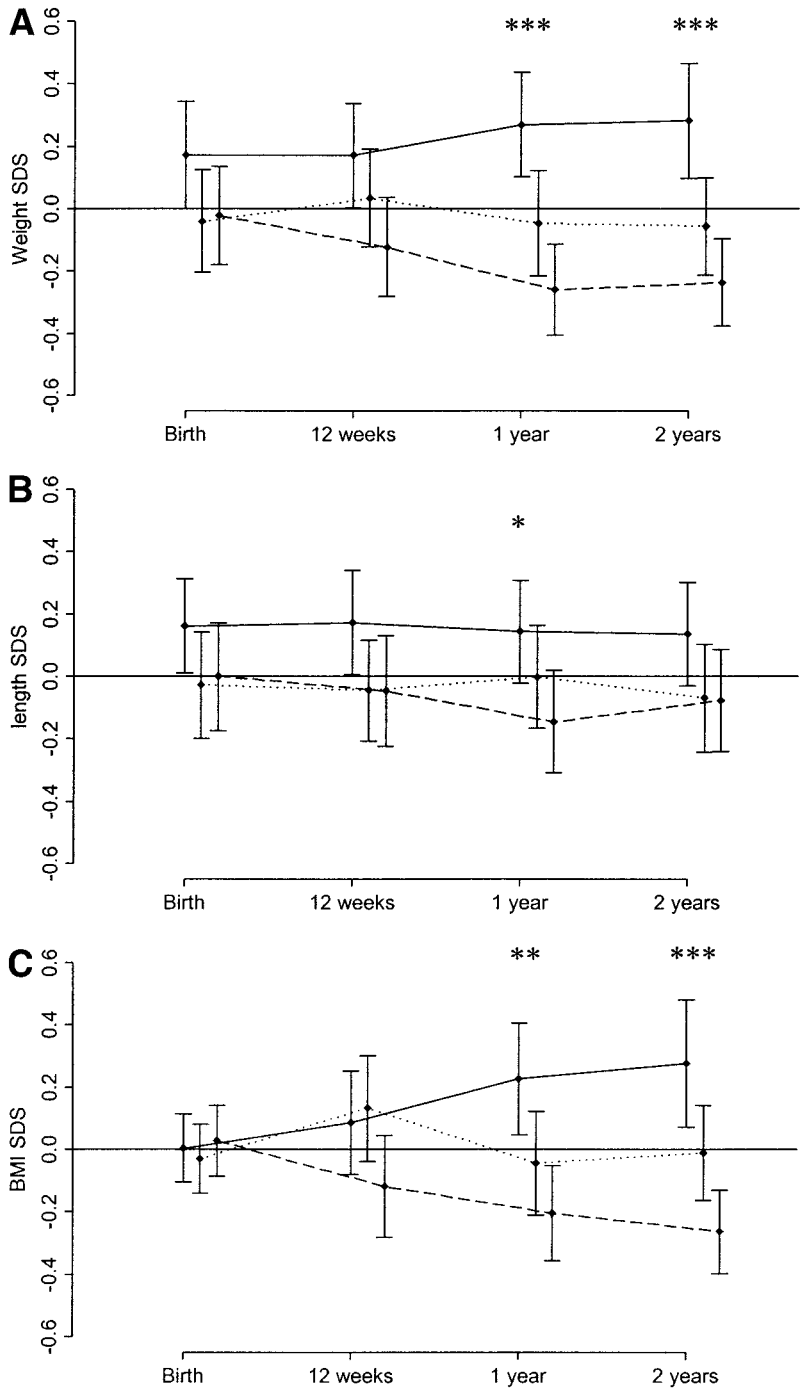

Figure 3—*Offspring weight* (A)*, length* (B)*, and BMI* (C) *in the first 2 years of life, shown according to tertiles of paternal BMI. Data are shown as mean SDS, corrected for sex and gestation (birth only), with 95% CI. Differences between tertiles were assessed at each time point using ANOVA.* *P < *0.05,* **P < *0.01,* ***P < *0.001. Solid line represents upper tertile, dotted line represents middle tertile, and dashed line represents lower tertile.*

lation, the impact of glycemia 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 glycemic 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 glycemia was not a major determinant of childhood obesity (22).

Maternal prepregnancy BMI was significantly correlated with birth weight ($r = 0.25$, $P < 0.001$). 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 2 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 glycemia. This supports the work of Simmons and Brier (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 birth weight 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 and 4 years, where the mother is obese in early pregnancy (26).

Maternal BMI had no association with birth length, while the association with child weight persisted, 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 that offspring of mothers with gestational diabetes have increased body fat, independent of birth weight (27).

In contrast to the maternal effects, paternal BMI has no effect on offspring birth weight 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 prepregnancy BMI. This is in contrast to two studies suggesting that parental anthropometry and child anthropometry were not related in the first 2 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 that 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 in-

dependent 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 1 year, parental attitudes toward 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.

In conclusion, we have demonstrated that the impact of maternal glycemia on birth weight, seen in our nondiabetic 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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