Newborn Size and Body Composition as Predictors of Insulin Resistance and Diabetes in the Parents

Parthenon Birth Cohort Study, Mysore, India

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OBJECTIVE—We aimed to examine detailed neonatal measurements as predictors of later diabetes in both parents.

RESEARCH DESIGN AND METHODS—Babies ($n = 617$) born to nondiabetic parents in Holdsworth Memorial Hospital, Mysore, India, were measured at birth for weight; crown-to-heel length (CHL), crown-to-rump length (CRL), and leg length; skinfolds (triceps and subscapular); and circumferences (head, abdomen, and mid–upper-arm circumference [MUAC]). Nine and a half years later, glucose tolerance and fasting insulin were measured in their parents (469 mothers and 398 fathers).

RESULTS—Sixty-two (15.6%) fathers and 22 (4.7%) mothers had developed diabetes. There were linear inverse associations of the children's birth weight, CHL, CRL, MUAC, and skinfolds with paternal diabetes and insulin resistance ($P < 0.05$ for all). Offspring birth weight and adiposity (MUAC, abdominal circumference, and skinfolds) showed U-shaped associations with maternal diabetes (P for quadratic association <0.05 for all). These associations persisted after adjusting for the parents' current adiposity and maternal glucose concentrations and adiposity during pregnancy. Newborn adiposity was positively related to maternal insulin resistance; this association was nonsignificant after adjusting for maternal current adiposity.

CONCLUSIONS—Newborn size is a window into the future health of the parents. Small newborn size (especially soft-tissue body components) predicts an increased risk of later diabetes in both parents, suggesting a genetic or epigenetic link between parents' diabetes risk and reduced fetal growth in their children. The association of higher birth weight and newborn adiposity with later maternal diabetes suggests effects on fetal adiposity of the intrauterine environment in prediabetic mothers.

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A number of studies have reported associations between low birth weight and risk of type 2 diabetes and cardiovascular disease in later life (1,2). Possible mechanisms include a programming effect of intrauterine undernutrition (the fetal origins hypothesis) (3) or common genetic factors that either increase insulin resistance or reduce insulin secretion, leading to both low birth weight and disease in later life (the fetal insulin hypothesis) (4). Several studies have reported that low offspring birth weight is related to an increased risk of cardiovascular disease and diabetes in either or both parents (5–10). These data are consistent with the fetal insulin hypothesis.

It is well known that babies born to mothers with gestational diabetes mellitus (GDM) tend to have higher birth weight because of an intrauterine overnutrition effect (11). Because mothers who develop GDM are at increased risk of developing diabetes in later life (12), this would create a positive relationship between offspring birth weight and risk of maternal diabetes. A combination of the above low–birth weight effect and the fetal overnutrition effect of maternal GDM could therefore result in a U-shaped relationship between offspring birth weight and risk of diabetes in mothers. Indeed such U-shaped associations have been reported in some studies (9,13). Of interest, these studies showed a U-shaped association even when mothers with GDM were excluded. Other studies, however, have found no association between offspring birth weight and maternal diabetes (14,15).

Studies examining the risk of diabetes in parents in relation to offspring birth size are mainly restricted to birth weight. Birth weight reflects a crude composite measure of bone, fat, muscle, and visceral mass. These components may have different relationships with long-term health outcomes in the parents. This may, in turn, shed light on the mechanisms involved. The Mysore Parthenon Study (16) has collected detailed neonatal anthropometric data as well as parental glucose tolerance data 9.5 years following the index pregnancy. Using this data, we aimed to examine detailed neonatal measurements as predictors of diabetes in the parents 9.5 years later in an Indian population.

RESEARCH DESIGN AND METHODS

Study population during pregnancy

Details of the Mysore Parthenon Study, a prospective birth cohort study initiated during 1997–1998, have been described earlier (16). In brief, 830 eligible women (no known history of diabetes, singleton pregnancy of <32 weeks' gestation) booking consecutively into the antenatal clinic at the Holdsworth Memorial Hospital (HMH), Mysore, India, took part in a study to investigate the incidence and

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determinants of GDM. GDM was diagnosed in 49 (6.2%) women. Of 830 women, 663 who chose to deliver at HMH gave birth to live babies without major anomalies and were included for additional follow-up.

Neonatal anthropometry

Detailed newborn anthropometry was performed according to a standard protocol, within 72 h of birth. Weight (birth weight) was measured using a digital weighing scale (Seca, Hamburg, Germany) and crown-to-heel length (CHL) and crown-to-rump length (CRL) using a Harpenden neonatal stadiometer (CMS Instruments, London, U.K.). Head circumference, abdominal circumference (at the level of the umbilicus), and mid–upper-arm circumference (MUAC) were measured with a blank tape, marked and measured against a fixed ruler. Skinfold thicknesses (triceps and subscapular) were measured using Harpenden skin-fold calipers (CMS Instruments). Leg length was derived by subtracting the CRL from the CHL. Arm muscle area (AMA) was calculated using the formula $[(\text{MUAC}-\pi\ \text{triceps})^2/4\pi]$ (17).

Follow-up of parents

Additional examination of these women and their husbands was based on the follow-up of their children. Children were seen annually until the age of 5 years and every 6 months thereafter. Of 663 births, 25 children died between birth and 5 years of age, 8 children with major medical problems were excluded from the study, and 91 families either declined to participate or moved away from Mysore, leaving 539 families (Fig. 1). Among 539 mothers, 2 had died, 12 were pregnant, and 6 declined to participate in the study, leaving 519 mothers; 17 fathers had died and 88 declined to participate in the study, leaving 434 fathers.

Mothers' and fathers' weight (Salter, Kent, U.K.) and height (Microtoise; CMS Instruments) and triceps, biceps, and subscapular and suprailiac skinfold thicknesses (Harpenden calipers; CMS Instruments) were measured using standardized methods. After an overnight fast, mothers and fathers with no known history of diabetes underwent a 2-h 75-g oral glucose tolerance test (World Health Organization protocol). Blood samples (fasting and 120-min post–glucose load) were collected for plasma glucose and insulin. A fasting blood sample only was collected for 21 mothers and 51 fathers who already were diagnosed as having diabetes. Samples

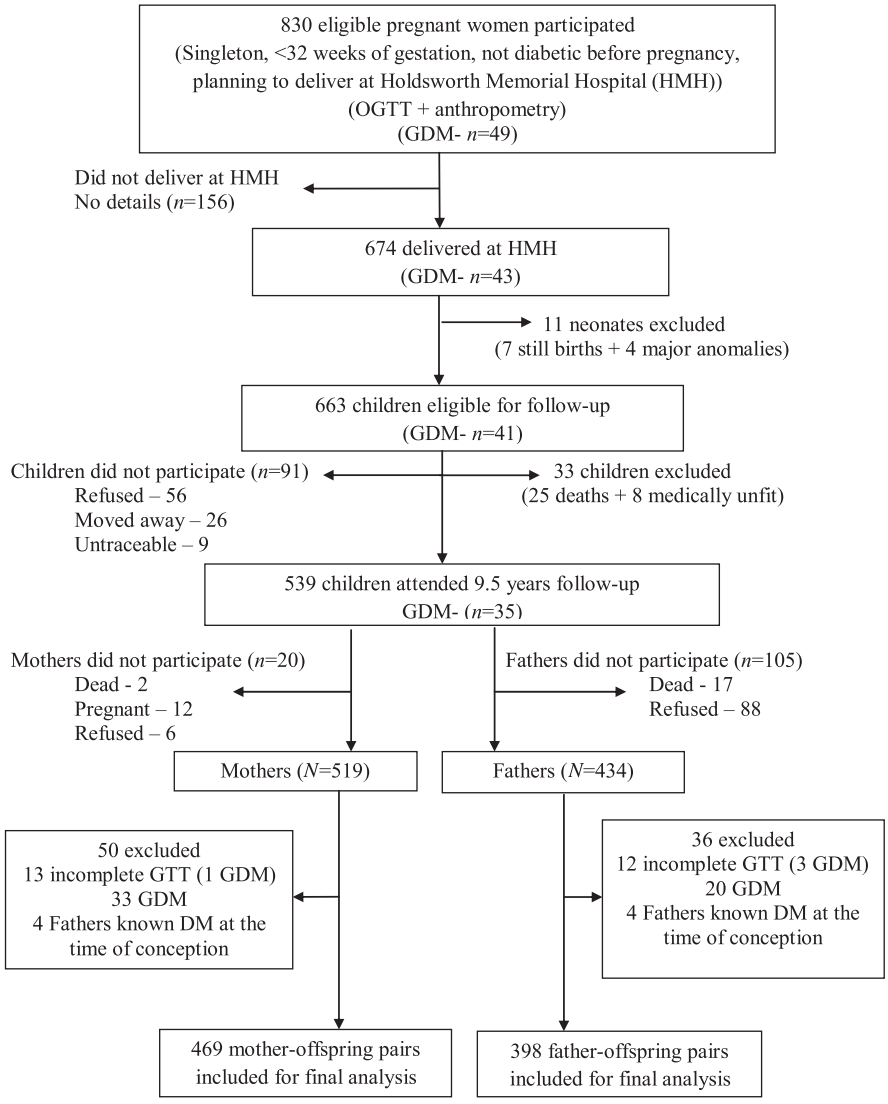

Figure 1—*Flow diagram describing study participants. DM, diabetes; GTT, glucose tolerance test; OGTT, oral glucose tolerance test.*

were stored at −80°C and analyzed at the end of data collection at the Diabetes Research Centre, KEM Hospital, Pune, after transfer from Mysore in dry ice.

Plasma glucose concentrations were measured by the glucose oxidase-peroxidase method (Alcyon 3000 Autoanlyzer; Abbott Laboratories); Interassay coefficients of variation were <5% for all. Insulin was measured using a time-resolved fluoroimmunoassay (Delfia; Wallac QY, Turku, Finland). Intra-assay and interassay coefficients of variation were 12.5% at <45 pmol/L and <10% at >45 pmol/L. Diabetes was defined as a fasting glucose concentration ≥7.0 mmol/L and/or a 120-min glucose ≥11.1 mmol/L (World Health Organization criteria) (18) and/or having been diagnosed with diabetes by a doctor since the index pregnancy. Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) equation (19). The HMH Research Ethics Committee approved the study, and informed verbal consent was obtained from the parents.

Analysis sample

We excluded 33 families in which the mother was diagnosed as having diabetes during the pregnancy with the index child, following an oral glucose tolerance test at 30 ± 2 weeks' gestation (none of the mothers were known to be diabetic before pregnancy). We also excluded four families in which the father was known to have diabetes (diagnosed by a doctor as having diabetes and was on antidiabetes medication) before the child's conception. An additional 13 mothers

and 12 fathers had incomplete glucose tolerance test data. This left 469 mother-offspring pairs and 398 father-offspring pairs in the analysis (Fig. 1).

Statistical methods

Variables with skewed distributions were log transformed (maternal and paternal biceps skinfold thickness, fasting and 120-min glucose, and fasting insulin and HOMA-IR). Associations of neonatal measurements with diabetes and HOMA-IR in their parents were analyzed by multiple logistic and linear regression, respectively adjusting for child's sex, gestational age, and the parent's current age (model 1) and further for the parent's current BMI and sum of skinfolds (model 2). Quadratic terms were used (birth measurement^2) to examine nonlinear associations between birth measurements and parental diabetes. Differences in associations between the sexes were examined using interaction terms (sex × birth measurement) in these regression models. Data were analyzed using Stata version 10 (Stata Corporation, College Station, TX).

RESULTS—Anthropometric characteristics of the offspring at birth and anthropometric and biochemical characteristics of the parents 9.5 years later are described in Table 1. At birth, boys were heavier, were longer, and had larger head circumferences and AMA than girls, whereas girls had larger triceps than boys (Table 1). There were no significant differences in neonatal measurements between babies whose parents did and did not take part in the study (data not shown). A total of 9% of fathers and 15% of mothers were obese (BMI >30 kg/m^2).

Sixty-two (15.6%; 45 known plus 17 new) fathers and 22 (4.7%; 7 known plus 15 new) mothers were found to have developed diabetes. In three families (<1%), both parents had developed diabetes; these were included in both mother-offspring and father-offspring analyses. Maternal and paternal age was positively correlated with their 120-min glucose concentrations (r = 0.1; P = 0.01 for both). Both parents' adiposity (BMI and sum of skinfolds) was positively correlated with their 120-min glucose and fasting insulin concentrations and HOMA-IR (r = 0.2–0.6; $P < 0.0001$ for all). The prevalence of diabetes among obese fathers was 22% compared with 15% among nonobese fathers and 8% among obese mothers compared with 4% in nonobese mothers.

Table 1—*Neonatal measurements, maternal and paternal anthropometry, and glucose/insulin parameters at 9.5 years following the index pregnancy*

Neonatal measurements	Male	Female	*P*
n	227	242	
Gestation (weeks)	38.9 (1.7)	39.2 (1.7)	0.09
Birth weight (kg)	2.893 (0.467)	2.795 (0.390)	0.01
CHL (cm)	48.8 (2.3)	48.3 (2.2)	0.01
CRL (cm)	32.0 (1.9)	31.7 (1.7)	0.04
Leg length (cm)	16.8 (1.4)	16.6 (1.5)	0.1
Head circumference (cm)	34.0 (1.4)	33.5 (1.3)	<0.0001
MUAC (cm)	10.3 (1.0)	10.2 (0.9)	0.3
AMA (cm^2)	6.5 (1.2)	6.3 (1.0)	0.04
Abdominal circumference (cm)	29.7 (2.1)	29.8 (1.9)	0.8
Triceps skinfold (mm)	4.1 (0.8)	4.2 (0.9)	0.046
Subscapular skinfold (mm)	4.3 (0.9)	4.5 (0.9)	0.1
Sum of skinfolds (mm)	8.4 (1.6)	8.7 (1.7)	0.06

Parents' characteristics	Mothers	Fathers
n	469	398
Age (years)	32.9 (3.9)	40.6 (4.6)
Anthropometry		
Height (cm)	154.6 (5.3)	167.9 (6.2)
Weight (kg)	60.7 (11.4)	70.8 (11.7)
BMI (kg/m^2)	25.4 (4.6)	25.1 (3.8)
Skinfold thickness		
Triceps (mm)	23.6 (8.2)	13.1 (5.5)
Biceps (mm)*	10.1 (6.5–13.2)	6.4 (4.9–8.7)
Subscapular (mm)	33.0 (11.7)	30.8 (11.9)
Suprailiac (mm)	27.4 (10.4)	26.5 (10.1)
Sum of skinfolds (mm)	94.4 (31.7)	77.2 (26.9)
Biochemical characteristics		
Glucose^0 (mmol/L)*	5.1 (4.8–5.4)	5.1 (4.7–5.6)
Glucose^{120} (mmol/L)*	6.1 (5.3–7.0)	6.0 (4.9–7.3)
Insulin^0 (pmol/L)*	46.8 (30.0–69.0)	47.4 (28.8–67.2)
Insulin resistance (HOMA-IR)*	1.8 (1.1–2.7)	1.9 (1.1–2.8)
Diabetes [*n* (%)]	22 (4.7) (15 new + 7 known)	62 (15.6) (17 new + 45 known)

Data are means (SD) or *n* (%) where indicated. *P* values are for the differences in birth characteristics between boys and girls, derived using *t* tests. *Transformed variable; data are median (interquartile range).

Associations of neonatal measurements with maternal and paternal diabetes

Among fathers, there were linear inverse associations of newborn birth weight, CHL, CRL, AMA, MUAC, and triceps, subscapular, and sum of skinfolds with prevalence of diabetes (Table 2). Among mothers, offspring birth weight and adiposity measures (MUAC and abdominal circumference and triceps, subscapular, and sum of skinfolds) showed U-shaped associations with diabetes prevalence. As in fathers, there was a linear inverse association of neonatal CHL with prevalence of maternal diabetes (Table 2). All these associations remained similar after adjustment for the parents' current BMI and sum of skinfolds (Table 2) and additionally for maternal gestational glucose concentrations and adiposity (sum of skinfolds) during pregnancy (data not shown). There were no associations of neonatal leg length and head circumference with either paternal or maternal diabetes. There were no sex interactions in the associations between offspring birth measurements and prevalence of parental diabetes.

Associations of newborn measurements with maternal and paternal insulin resistance

There were inverse associations of all the newborn measurements except leg length

Table 2—*Associations of neonatal measurements with paternal and maternal diabetes 9.5 years following the index pregnancy*

Offspring birth measurements	Paternal diabetes according to quintiles of neonatal measurements [*n* (%)]					Multiple logistic regression			
						OR (95% CI)	*P**	OR (95% CI)	*P*†
n	76	90	84	78	70				
Birth weight (kg)	19 (25.0)	14 (15.6)	14 (16.7)	9 (11.5)	6 (8.6)	0.4 (0.18–0.76)	0.007	0.3 (0.13–0.65)	0.002
CHL (cm)	19 (23.5)	15 (16.9)	11 (13.8)	12 (15.6)	5 (7.0)	0.8 (0.72–0.95)	0.006	0.8 (0.70–0.93)	0.003
CRL (cm)	21 (26.9)	17 (19.1)	9 (10.6)	6 (7.7)	9 (13.2)	0.8 (0.65–0.92)	0.005	0.8 (0.63–0.93)	0.006
Leg length (cm)	10 (12.4)	18 (19.0)	15 (18.1)	10 (14.7)	9 (12.7)	0.9 (0.78–1.12)	0.5	0.9 (0.74–1.07)	0.2
Head circumference (cm)	17 (22.7)	12 (12.9)	12 (16.7)	15 (19.7)	6 (7.3)	0.8 (0.67–1.05)	0.1	0.8 (0.66–1.05)	0.1
MUAC (cm)	20 (22.0)	15 (19.0)	14 (16.5)	8 (10.7)	5 (7.4)	0.6 (0.46–0.87)	0.005	0.6 (0.42–0.83)	0.002
AMA (cm^2)	20 (24.4)	10 (12.1)	17 (21.5)	8 (10.7)	7 (8.9)	0.7 (0.54–0.95)	0.02	0.7 (0.52–0.92)	0.01
Abdominal circumference (cm)	16 (19.3)	16 (18.6)	14 (16.1)	10 (13.9)	6 (8.6)	0.9 (0.77–1.02)	0.09	0.9 (0.74–1.01)	0.06
Triceps skinfold (mm)	22 (22.9)	14 (19.7)	18 (18.2)	4 (6.2)	4 (6.0)	0.6 (0.38–0.80)	0.002	0.5 (0.35–0.77)	0.001
Subscapular skinfold (mm)	15 (18.3)	19 (20.4)	15 (19.7)	9 (10.8)	4 (6.3)	0.6 (0.43–0.88)	0.008	0.6 (0.40–0.85)	0.005
Sum of skinfolds (mm)	18 (21.7)	17 (19.8)	15 (17.9)	9 (11.1)	3 (4.7)	0.7 (0.60–0.89)	0.002	0.7 (0.57–0.87)	0.001

Offspring birth measurements	Maternal diabetes according to quintiles of neonatal measurements [*n* (%)]					Multiple logistic regression					
						OR (95% CI)	*P**	OR (95% CI)	*P*†	*P*‡	*P*§
n	92	106	101	88	82						
Birth weight (kg)	8 (8.7)	2 (1.9)	3 (3.0)	3 (3.4)	6 (7.3)	0.8 (0.25–2.30)	0.6	0.5 (0.16–1.52)	0.2	0.01	0.02
CHL (cm)	8 (8.6)	2 (1.9)	4 (4.2)	6 (6.4)	2 (2.4)	0.8 (0.70–1.02)	0.09	0.8 (0.67–0.99)	0.04	0.7	0.7
CRL (cm)	6 (6.3)	5 (5.1)	3 (3.1)	7 (6.9)	1 (1.3)	0.8 (0.65–1.09)	0.2	0.8 (0.63–1.05)	0.1	0.8	0.6
Leg length (cm)	6 (6.6)	5 (4.6)	7 (6.9)	1 (1.2)	3 (3.8)	0.9 (0.67–1.14)	0.3	0.9 (0.66–1.13)	0.3	0.7	0.7
Head circumference (cm)	6 (6.7)	3 (2.8)	4 (4.6)	3 (3.1)	6 (6.9)	1.0 (0.71–1.43)	0.9	0.9 (0.67–1.36)	0.8	0.3	0.2
MUAC (cm)	5 (4.7)	2 (2.1)	8 (7.7)	3 (3.4)	4 (5.3)	1.0 (0.61–1.61)	0.9	0.8 (0.51–1.37)	0.5	0.03	0.046
AMA (cm^2)	4 (4.2)	5 (4.9)	2 (2.1)	6 (7.0)	5 (5.6)	1.0 (0.64–1.46)	0.9	0.9 (0.56–1.31)	0.5	0.1	0.2
Abdominal circumference (cm)	6 (6.2)	4 (4.1)	4 (4.2)	2 (2.2)	6 (7.0)	1.0 (0.78–1.21)	0.8	0.9 (0.71–1.14)	0.4	0.004	0.009
Triceps skinfold (mm)	8 (7.1)	3 (3.3)	4 (3.6)	2 (2.6)	5 (6.6)	1.2 (0.72–1.90)	0.5	1.0 (0.58–1.60)	0.9	0.005	0.006
Subscapular skinfold (mm)	4 (4.3)	7 (6.3)	3 (3.3)	3 (3.1)	5 (6.8)	1.4 (0.88–2.11)	0.2	1.1 (0.73–1.80)	0.5	0.02	0.02
Sum of skinfolds (mm)	5 (5.2)	7 (6.3)	1 (1.1)	5 (5.3)	4 (5.3)	1.1 (0.90–1.46)	0.3	1.0 (0.80–1.33)	0.8	0.007	0.008

Odds ratios (ORs) and *P* values are derived using logistic regression. **P* adjusted for child's sex, gestational age, and parents' current age. †*P* adjusted for child's sex, gestational age, parents' current age, and current adiposity (BMI and sum of skinfolds). ‡*P* value for quadratic association between neonatal measurements and maternal diabetes, adjusted for the child's sex, gestational age, and mother's current age. §*P* value for quadratic association between neonatal measurements and maternal diabetes after additional adjustment for mother's current adiposity (BMI and sum of skinfolds).

with paternal HOMA-IR after adjusting for current paternal adiposity (Table 3). These associations persisted after additional adjustment for maternal adiposity and glucose concentrations during pregnancy (data not shown).

Among mothers there were positive associations of neonatal birth weight, head circumference, AMA, and adiposity measures (MUAC and subscapular and sum of skinfolds) with maternal HOMA-IR (Table 3). All these associations were attenuated and no longer significant after adjustment for maternal current adiposity (Table 3). There were no associations of CHL, CRL, leg length, abdominal circumference, and triceps with maternal HOMA-IR. Although there was some evidence of U-shaped associations (the highest values in the highest and lowest birth-size groups for birth weight, MUAC, and AMA) (Table 3), there were no significant nonlinear relationships or sex interactions in the associations of offspring birth measurements with either paternal or maternal HOMA-IR (Table 3).

CONCLUSIONS—In this prospective study of both parents, who were nondiabetic at the time of the pregnancy, we found an inverse relationship between measurements of their newborn babies and their diabetes risk 9.5 years later. Smaller newborn size, especially smaller soft-tissue measurements (weight, MUAC/AMA, and skinfolds), was associated with an increased risk of diabetes in both parents and higher insulin resistance in fathers. In addition, higher birth weight and greater newborn adiposity predicted an increased risk of maternal diabetes, resulting in clear U-shaped associations between these newborn measurements and maternal diabetes risk. These findings persisted after adjusting for potential confounding variables. There were positive associations of neonatal birth weight, head circumference, AMA, and adiposity measures with maternal HOMA-IR, which seemed to be mediated by maternal current adiposity.

Strengths of the study were its prospective design with continuous follow-up of the children, which enabled us to examine the glucose/insulin metabolism of their parents. Apart from birth weight, detailed neonatal anthropometric data were available that were based on direct measurements using standardized methods and not on recall. A limitation was loss to follow-up, which could have introduced selection bias. However, a high proportion of the original cohort (76% of mother-infant pairs and 64% of father-infant pairs) was followed-up, and children's birth measurements were similar among those whose parents did or did not participate in the study.

Our finding of an inverse association between neonatal birth weight and paternal diabetes and insulin resistance is not new and is consistent with earlier studies in the U.K. (4,5), the U.S. (6), and Sweden (7,8). As described in the introduction, this is consistent with the fetal insulin hypothesis, whereby genes associated with impaired insulin secretion or sensitivity, and shared by both father and fetus, could result in impaired fetal growth and increased diabetes risk in the father. A number of genetic polymorphisms have been related to both newborn size and diabetes risk. Many studies, including a genome-wide association meta-analysis and review, identified specific gene markers that are associated with reduced birth weight (20,21) or increased susceptibility to diabetes (22,23) or both (21,24,25). Evidence from white populations suggests that the genetic markers ADCY5, glucokinase, KCNJ11, CDKAL1, and HHEX-IDE are associated with both diabetes and lower birth weight by reducing insulin secretion (21,24,25). An alternative possibility to the fetal insulin hypothesis is that epigenetic changes in the sperm of men at risk for diabetes also can lead to reduced fetal growth. Although there is no data to support this in humans, animal studies suggest that epigenetic changes can be transmitted by fathers as well as mothers and may mediate effects of preconceptional paternal diet on metabolic parameters in the offspring (26).

Our finding of a U-shaped relationship between offspring birth weight and maternal diabetes is similar to a study among 60- to 79-year-old women in the U.K. (14) and another among Swedish women (7). The lower part of the "U" could reflect the same genetic or epigenetic phenomenon described above for fathers, whereas the upper part of the "U" could reflect effects on fetal development of the intrauterine environment in a prediabetic mother. Offspring born to mothers with gestational glucose intolerance are macrosomic (12); following the delivery, these mothers develop insulin resistance and are at increased risk of developing diabetes later (13). Alternatively (reverse causality), variations in the fetal genome that alter fetal growth also could alter maternal appetite and metabolism (for example a larger fetus and placenta may stimulate greater maternal food intake), and this could lead to insulin resistance and glucose intolerance during pregnancy and a higher diabetes risk later (27,28). Previously reported associations between offspring birth weight and diabetes risk among mothers have been quite variable; therefore, although two studies have reported a U-shaped association (7,14), others have reported a linear inverse association (4), two have reported a linear positive association (6,8), and two found no association (10,11). Whether a U-shape is present or whether one or other arms of the "U" predominate would depend upon the prevalence of relevant genetic/epigenetic markers and the prevalence of gestational diabetes within particular populations. One of two studies reporting a positive association between birth weight and maternal diabetes was in the Pima Indians, who have exceptionally high rates of GDM (6). The same would be true of associations between maternal insulin resistance and offspring birth weight. In our study, this was a significant positive association, although there was evidence of a weak U-shape, consistent with the diabetes results.

Striking exceptions to the neonatal measurements that were inversely related to diabetes risk in both parents were leg length and head circumference, which are both direct measurements of skeletal size. The newborn body components most consistently related to parental diabetes were the soft-tissue measurements (apart from birth weight, MUAC, AMA, skinfolds, and abdominal circumference). CHL and CRL also were inversely associated with diabetes in the parents, but this could reflect newborn fat or muscle, which influence these measurements on a stadiometer, especially CRL, because of increased buttock size. The main growth-promoting hormones during intrauterine life are insulin and IGF-I and IGF-II (29,30). Evidence from infusion experiments in animals suggests that insulin directly promotes the growth of fetal adipose and skeletal tissue, whereas IGF-I stimulates skeletal, but not adipose tissue, growth (30). The IGFs also have been linked to a lower diabetes risk (31). Our findings are therefore in keeping with an effect mediated by reduced insulin action or secretion, rather than IGF action/secretion. To conclude, in this Indian population, smallness in all body components at birth, except leg length and head circumference,

Table 3—*Associations of neonatal measurements with paternal and maternal insulin resistance (HOMA-IR)* 9.5 years following the index pregnancy*

Offspring birth measurements	Paternal insulin resistance (HOMA-IR)* according to quintiles of neonatal measurements [median (interquartile range)]					Multiple linear regression			
						β (95% CI)	*P*†	β (95% CI)	*P*‡
n	76	90	84	78	70				
Birth weight (kg)	1.8 (1.0–3.3)	1.8 (1.0–2.4)	1.8 (1.1–2.6)	2.0 (1.1–2.7)	1.9 (1.1–3.1)	0.003 (−0.20 to 0.20)	0.9	−0.3 (−0.44 to −0.12)	0.001
CHL (cm)	1.8 (1.0–2.7)	2.0 (1.2–2.8)	1.8 (0.9–2.8)	1.7 (1.0–2.9)	1.9 (1.1–2.5)	−0.02 (−0.05 to 0.02)	0.4	−0.04 (−0.08 to −0.01)	0.005
CRL (cm)	1.8 (1.0–2.8)	1.9 (1.3–2.9)	1.8 (1.0–2.5)	1.8 (1.1–2.5)	2.0 (1.1–3.2)	0.00004 (−0.05 to 0.05)	1.0	−0.05 (−0.09 to −0.01)	0.02
Leg length (cm)	1.9 (1.0–2.6)	2.0 (1.2–3.2)	1.9 (1.1–2.7)	1.7 (0.9–3.0)	1.8 (1.1–2.6)	−0.03 (−0.09 to 0.02)	0.3	−0.03 (−0.07 to 0.02)	0.2
Head circumference (cm)	1.8 (0.9–3.1)	1.8 (1.2–2.6)	1.8 (1.0–2.7)	1.9 (1.1–2.7)	2.0 (1.1–3.1)	−0.003 (−0.07 to 0.06)	0.9	−0.06 (−0.12 to −0.01)	0.02
MUAC (cm)	2.0 (0.9–3.0)	1.7 (1.0–2.4)	2.0 (1.1–2.9)	1.8 (1.0–2.5)	1.9 (1.1–2.8)	−0.03 (−0.11 to 0.06)	0.6	−0.1 (−0.19 to −0.05)	0.001
AMA (cm^2)	2.1 (0.9–3.1)	1.7 (1.0–2.4)	1.9 (1.2–2.5)	1.9 (1.1–2.9)	1.7 (1.0–2.8)	−0.02 (−0.09 to 0.06)	0.6	−0.09 (−0.15 to −0.03)	0.005
Abdominal circumference (cm)	2.1 (0.9–3.2)	1.9 (1.0–2.6)	1.9 (1.2–2.6)	1.7 (1.1–2.6)	1.8 (1.0–2.8)	−0.01 (−0.05 to 0.03)	0.6	−0.05 (−0.09 to −0.02)	0.002
Triceps skinfold (mm)	2.0 (1.1–3.2)	2.0 (1.2–2.7)	1.9 (0.9–2.6)	1.6 (1.0–2.4)	2.0 (1.1–2.6)	−0.02 (−0.12 to 0.07)	0.6	−0.1 (−0.19 to −0.04)	0.003
Subscapular skinfold (mm)	1.8 (0.9–2.8)	2.0 (1.1–2.8)	1.8 (1.1–2.5)	1.9 (1.1–2.9)	1.6 (1.0–2.6)	−0.03 (−0.12 to 0.06)	0.6	−0.1 (−0.18 to −0.03)	0.004
Sum of skinfolds (mm)	1.8 (1.0–3.2)	1.9 (1.1–2.6)	2.0 (1.2–2.7)	1.7 (0.9–2.4)	1.8 (1.1–2.6)	−0.01 (−0.06 to 0.03)	0.6	−0.06 (−0.11 to −0.02)	0.002

Offspring birth measurements	Maternal insulin resistance (HOMA-IR)* according to quintiles of neonatal measurements [median (interquartile range)]					Multiple linear regression					
						β (95% CI)	*P*†	OR (95% CI)	*P*‡	*P*§	*P*¶
n	92	106	101	88	82						
Birth weight (kg)	1.8 (1.1–2.5)	1.7 (1.1–2.4)	1.7 (1.1–2.7)	1.7 (1.1–2.8)	2.1 (1.1–3.1)	0.2 (0.06–0.36)	0.007	0.03 (−0.10 to 0.17)	0.6	0.5	0.2
CHL (cm)	1.8 (1.1–2.5)	1.7 (1.1–2.4)	1.8 (1.1–2.5)	1.9 (1.3–2.9)	1.7 (1.0–2.9)	0.01 (−0.02 to 0.04)	0.6	−0.01 (−0.03 to 0.02)	0.6	0.1	0.3
CRL (cm)	1.7 (1.1–2.3)	1.8 (1.1–2.6)	1.7 (1.1–2.5)	1.8 (1.1–2.9)	1.9 (1.1–2.8)	0.01 (−0.02 to 0.05)	0.5	−0.01 (−0.04 to 0.02)	0.6	0.2	0.2
Leg length (cm)	1.7 (1.1–2.5)	1.8 (1.1–3.0)	1.8 (1.1–2.4)	1.8 (1.0–2.7)	1.7 (1.1–2.8)	0.001 (−0.04 to 0.04)	0.9	−0.002 (−0.04 to 0.03)	0.9	0.4	0.9
Head circumference (cm)	1.7 (1.0–2.4)	1.6 (1.1–2.4)	1.9 (1.1–2.8)	1.8 (1.2–2.9)	2.1 (1.1–3.1)	0.06 (0.01–0.11)	0.03	0.03 (−0.02 to 0.07)	0.2	0.07	0.03
MUAC (cm)	1.8 (1.1–2.5)	1.7 (1.0–2.5)	1.7 (1.2–2.5)	1.8 (1.1–2.6)	2.1 (1.2–3.3)	0.08 (0.01–0.15)	0.02	0.02 (−0.04 to 0.08)	0.5	0.9	0.4
AMA (cm^2)	1.9 (1.1–2.5)	1.7 (1.1–2.5)	1.8 (1.2–2.4)	1.7 (1.0–2.7)	2.1 (1.1–3.1)	0.06 (0.003–0.12)	0.04	0.02 (−0.03 to 0.07)	0.4	0.9	0.6
Abdominal circumference (cm)	1.7 (1.0–2.3)	1.8 (1.3–2.8)	1.8 (1.2–2.6)	1.8 (1.1–2.8)	1.9 (1.0–3.1)	0.03 (−0.002 to 0.06)	0.07	0.002 (−0.02 to 0.03)	0.9	0.5	0.5
Triceps skinfold (mm)	1.7 (1.0–2.7)	1.8 (1.3–2.5)	1.7 (1.0–2.5)	1.8 (1.1–2.6)	2.1 (1.2–3.0)	0.07 (−0.001 to 0.14)	0.054	−0.01 (−0.07 to 0.05)	0.8	0.3	0.4
Subscapular skinfold (mm)	1.7 (0.8–2.4)	1.9 (1.3–2.8)	1.7 (1.2–2.5)	1.9 (1.0–2.9)	1.8 (1.1–3.1)	0.08 (0.01–0.15)	0.03	−0.004 (−0.07 to 0.06)	0.9	0.9	0.8
Sum of skinfolds (mm)	1.6 (1.0–2.5)	1.8 (1.2–2.5)	1.8 (1.1–2.6)	1.8 (1.0–2.9)	1.9 (1.2–3.1)	0.04 (0.01–0.08)	0.03	−0.004 (−0.04 to 0.03)	0.8	0.6	0.8

*Logged variable; β (the regression coefficient indicates percentage change in the outcome per unit change in the predictor) and *P* values are derived using linear regression. †*P* adjusted for child's sex, gestational age, and parents' current age. ‡*P* adjusted for child's sex, gestational age, parents' current age, and current adiposity (BMI and sum of skinfolds). §*P* value for quadratic association between neonatal measurements and maternal HOMA-IR adjusted for the child's sex, gestational age, and mother's current age. ¶*P* value for quadratic association between neonatal measurements and maternal HOMA-IR after additional adjustment for mother's current adiposity (BMI and sum of skinfolds).

predicts an increased risk of later diabetes in both parents; this suggests a genetic or epigenetic link between diabetes risk in either parent and reduced fetal growth in their children. In addition, higher birth weight and greater newborn adiposity predict an increased risk of maternal diabetes; this suggests either that prediabetic metabolic changes in the mother during pregnancy (other than her glucose concentrations) increase fetal adiposity or that fetal adiposity induces maternal diabetes. This study adds to very few other studies that have shown these two effects so clearly.

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S.R.V. participated in the collection, analysis, and interpretation of the data and wrote the manuscript. G.V.K. participated in data collection and reviewed and edited the manuscript. C.H.F. contributed to the discussion and reviewed and edited the manuscript. S.R.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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