Higher Offspring Birth Weight Predicts the Metabolic Syndrome in Mothers but Not Fathers 8 Years After Delivery

The Pune Children's Study

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In Europid populations, low birth weight of offspring predicts insulin resistance in the mother and cardiovascular disease in both parents. We investigated the association between birth weight of offspring and obesity and cardiovascular risk in the parents of 477 8-year-old children born at the King Edward Memorial Hospital, Pune, India. Eight years after the birth of the child, mothers (33 years of age, $n = 459$) of heavier babies were taller and more obese (BMI, fat mass, and waist circumference, all $P < 0.001$) than mothers of lighter babies. Increasing offspring birth weight predicted higher homeostasis model assessment for insulin resistance ($P < 0.01$) and metabolic syndrome in mothers ($P < 0.001$) (adjusted for offspring sex and birth order, maternal age, and socioeconomic status) but not hyperglycemia. Fathers (39 years of age, $n = 398$) of heavier babies were taller and heavier, independent of maternal size ($P < 0.01$, both), but were not more insulin resistant. Unlike other reports, lower offspring birth weight did not predict insulin resistance in fathers. Thus, urban Indian parents have a higher risk of being obese 8 years after delivery of a heavier child. Mothers but not fathers of heavier babies also have a higher risk of being insulin resistant and developing the metabolic syndrome. Our findings highlight the need for a better understanding of the relation between fetal growth and future health before contemplating public health interventions to improve fetal growth. *Diabetes* 52:2090–2096, 2003

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CHD, coronary heart disease; GDM, gestational diabetes mellitus; HOMA, homeostasis model assessment; HOMA-IR, HOMA for insulin resistance; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; SES, socioeconomic status; WHR, waist-to-hip ratio.

There is growing interest in the association between size at birth and the risk of diabetes and cardiovascular disease in later life (1). Size at birth reflects intrauterine growth, which is determined by intrauterine environment as well as genetic factors. Diabetes is more common in those who are small or large at birth (2,3). Studies that show an inverse relation between birth weight and insulin resistance syndrome (metabolic syndrome) have been interpreted to mean that "fetal undernutrition" is the causative factor (the "thrifty phenotype" hypothesis) (4). The "fetal insulin hypothesis" offers an alternative genetic explanation for the relationship (5). Davey-Smith et al. (6) have explored another aspect of this relationship. They showed that offspring low birth weight is associated with increased cardiovascular risk in parents (6–8), increased maternal insulin resistance during late adulthood (9), and diabetes in fathers (10). They favor a genetic explanation for their findings. On the other hand, large babies born to mothers with gestational diabetes mellitus (GDM) have an increased risk of diabetes (11,12), and mothers also have an increased risk of diabetes (13). Maternal insulin resistance during (late) gestation is an important mechanism to divert nutrients (glucose, amino acids, and triglycerides/fatty acids) to the fetus to promote growth (14). Offspring birth weight could be used as a useful surrogate for maternal metabolism in pregnancy. In recent years there has been a growing recognition that pregnant metabolic state and events provide a window into future maternal risk of disease (15).

In the Pune Children's Study, we investigated the determinants of insulin resistance in 8-year-old urban children (16). At the same time, we measured body size, insulin resistance, and other cardiovascular risk factors in their parents. We report the relationship between the child's birth weight and parental measurements.

RESEARCH DESIGN AND METHODS

Details of our methods have been reported previously (16). Of 477 families, 6 mothers and 12 fathers had died, and 459 (nonpregnant) mothers and 398 fathers agreed to be studied. Standardized anthropometric measurements were made by one of two trained observers. Fat mass was calculated from four skinfold-thickness measurements using Durnin's formula (17). Blood

TABLE 1
Anthropometric and biochemical measurements in parents of 8-year-old children

	Mothers	Fathers
n	456	398
Age (years)	33 (30–35)	39 (36–42)
Anthropometry		
Height (cm)	153.0 (150.0–157.0)	165.8 (162.3–170.3)
Weight (kg)	52.0 (44.5–59.8)	63.0 (55.8–70.0)
BMI (kg/m^2)	22.1 (18.9–25.3)	22.8 (20.7–25.4)
WHR	0.76 (0.71–0.81)	0.91 (0.86–0.94)
Body fat (%)	33.6 (27.6–37.6)	25.3 (21.3–28.2)
Glucose-insulin		
Fasting plasma glucose (mmol/l)	4.8 (4.4–5.4)	5.0 (4.4–5.6)
30-min plasma glucose (mmol/l)	7.8 (6.7–8.8)	8.2 (6.9–9.3)
120-min plasma glucose (OGTT) (mmol/l)	5.5 (4.7–6.7)	6.1 (5.0–7.7)
Fasting plasma insulin (pmol/l)	34.0 (22.0–50.0)	35.0 (21.0–51.0)
30-min plasma insulin (pmol/l)	199.0 (123.0–308.5)	195.0 (103.5–319.0)
120-min plasma insulin (pmol/l)	176.5 (102.7–308.2)	214.0 (107.0–425.0)
Plasma split 32-33 insulin (pmol/l)	6.3 (3.9–9.8)	12.0 (7.6–22.0)
Plasma proinsulin (pmol/l)	4.1 (3.0–5.8)	7.8 (4.9–13.0)
HOMA-IR	1.42 (0.96–2.13)	1.94 (1.15–3.10)
Lipids		
Total cholesterol (mmol/l)	3.8 (3.3–4.4)	4.2 (3.6–5.0)
HDL cholesterol (mmol/l)	1.0 (0.8–1.2)	0.9 (0.7–1.1)
Triglycerides (mmol/l)	0.8 (0.6–1.2)	1.2 (0.9–1.9)
Blood pressure		
Systolic (mmHg)	120 (113–127)	129 (122–137)
Diastolic (mmHg)	71 (65–78)	77 (71–84)

Data are median (interquartile range).

pressure was measured using a digital automated device (Dinamap; Criticon, Tampa, FL) after 10-min rest in the supine position.

A 75-g anhydrous oral glucose tolerance test (OGTT) was performed on subjects not on antidiabetic treatment. Three venous blood samples (fasting and at 30 and 120 min after oral glucose) were collected for measurement of plasma glucose and insulin concentrations. Plasma cholesterol, HDL cholesterol, triglycerides, proinsulin, and 32-33 split proinsulin were measured in the fasting sample by standard methods. Insulin resistance was calculated using the homeostasis model assessment (HOMA) (18), and the 30-min insulin increment was used as an estimate of β-cell function (19). Metabolic syndrome was defined following World Health Organization guidelines (20), except that the BMI cutoff point for obesity was 25 kg/m^2 rather than 30 kg/m^2 because of the recent recognition of a need to revise BMI criteria for Asian populations (21). Those in the highest quartile of HOMA for insulin resistance (HOMA-IR) were diagnosed as insulin resistant. Metabolic syndrome was diagnosed if a subject had a fasting plasma glucose concentration ≥6.1 mmol/l or a 120-min concentration ≥7.8 mmol/l and/or were insulin resistant and in addition had two or more of the following: *1*) BMI ≥25 kg/m^2 and/or waist-hip ratio ≥0.90 for men and ≥0.85 for women, *2*) plasma triglyceride concentration ≥1.7 mmol/l and/or HDL cholesterol <0.9 mmol/l for men and <1.0 mmol/l for women, and *3*) blood pressure ≥140/90 mmHg.

Socioeconomic status (SES) was assessed using the Kuppuswamy score (22), a standardized scoring system based on a questionnaire asking for details of occupation, education, income, and size and type of housing. Each aspect is separately scored, and the scores are added to get a total socioeconomic score (a high value indicates prosperity). History of smoking and alcohol consumption was recorded as never, past, and current.

Statistical methods. Variables not normally distributed were log transformed to satisfy assumptions of normality and are represented in the tables by the geometric mean. For convenience of interpretation, we have shown the distribution of parental characteristics by sex-specific thirds of their child's birth weight. However, in the analyses, birth weight and parental measurements were used as continuous variables. The significance of the relation between the child's birth weight and parental characteristics was tested by linear regression analysis, adjusting for possible confounders (child's sex and birth order, parental age, SES, and BMI). The significance of the relation between the child's birth weight and categorical outcomes (obesity, diabetes, hypertension, metabolic syndrome, etc.) was tested using logistic regression.

RESULTS

The mean birth weights of the children were 2.8 kg (boys) and 2.6 kg (girls). Their birth weight distribution was similar to that for all babies born in the hospital during the same time period. There was no significant difference in birth weight of children whose parents were studied or not studied. Birth weight increased with the birth order of the child ($P < 0.001$), but was not related to the SES of the family ($P = 0.42$).

Parents. Table 1 shows the characteristics of the parents. Tables 2 and 3 show maternal and paternal size and cardiovascular risk factors by thirds of their child's birth weight.

Mothers. One mother was known to be diabetic before pregnancy and died 5 years after delivery. Her child and his father are excluded from the analysis.

The OGTT was not routinely performed during pregnancy, but 13 mothers were diagnosed as having GDM by the treating obstetrician on clinical indications; none of them were on antidiabetic treatment at the time of this study. OGTTs were performed in 456 mothers, of whom 16 showed diabetes (6 were previously diagnosed GDM) and 45 showed impaired glucose tolerance (IGT).

Anthropometric measurements were available in 459 mothers. Altogether, 27% had BMI >25 kg/m^2, 10% had waist-to-hip ratio (WHR) >0.85, and 42% had body fat >35% (Table 2). All indices of obesity (BMI, waist circumference, WHR, and body fat mass and percentage) were positively related to circulating concentrations of glucose and insulin (fasting and 30 and 120 min), triglycerides, and total cholesterol and inversely related to HDL cholesterol. HOMA-IR was strongly related to all the indices of obesity

TABLE 2
Maternal size, glucose/insulin variables, and maternal morbidity 8 years after delivery according to sex-specific thirds of offspring birthweight

	Offspring birth weight tertile (sex-specific)			Adjusted for					
	1 (n = 154)	2 (n = 152)	3 (n = 153)	Maternal age, offspring sex	P	+Offspring birth order (P)	+SES (P)	+Maternal BMI (P)	
Birth weight (kg)	2.26	2.75	3.28						
Anthropometry									
Height (cm)	151.4	153.6	154.4	2.77 (1.62–3.92)	0.001	0.001	0.001		
Weight (kg)	49.5	51.9	55.7	5.37 (3.34–7.41)	0.001	0.001	0.001		
BMI (kg/m^2)	21.6	22.0	23.3	1.47 (0.64–2.30)	0.001	0.001	0.001		
Waist (cm)	70.7	72.3	76.1	4.33 (2.26–6.41)	0.001	0.001	0.001		
WHR	0.76	0.76	0.78	0.02 (0.004–0.03)	0.014	0.009	0.019		
Fat mass (kg)	15.9	17.1	19.3	2.98 (1.74–4.23)	0.001	0.001	0.001		
Head circumference (cm)	52.8	53.0	53.3	0.56 (0.26–0.86)	0.001	0.001	0.001		
Glucose/insulin									
Fasting plasma glucose (mmol/l)	4.9	4.8	5.0	1.5* (−3.0 to 5.1)	0.46	0.48	0.74	−0.3 (−4.8 to 4.1)*	0.86
2-h plasma glucose (OGTT) (mmol/l)	5.6	5.5	6.0	4.0* (−3.0 to 11.6)	0.21	0.26	0.47	−1.0 (−7.7 to 6.0)*	0.76
Fasting Plasma Insulin (pmol/l)	26.8	31.5	34.7	27.0* (9.4–47.6)	0.002	0.002	0.007	16.2 (−1.0 to 35.0)*	0.07
30-min insulin increment	3.2	4.8	4.5	0.70 (−0.88 to 2.28)	0.38	0.39	0.47	0.47 (−1.27 to 2.2)	0.61
Plasma split 32-33 insulin (pmol/l)	6.2	6.2	6.8	10.5* (−4.9 to 28.4)	0.17	0.28	0.71	−5.8 (−18.9 to 8.3)*	0.35
Plasma proinsulin (pmol/l)	4.2	4.2	4.3	0.5* (−10.4 to 12.7)	0.93	0.89	0.65	−8.6 (−19.0 to 1.0)*	0.08
HOMA-IR	1.28	1.42	1.61	22.1* (7.2–41.9)	0.004	0.005	0.025	7.2 (−5.8 to 23.4)*	0.29
Glucose/insulin excluding IGT and diabetes									
Fasting plasma glucose (mmol/l)	4.7	4.7	4.5	1.5* (−2.0 to 5.1)	0.38	0.30	0.39	1.0 (−2.0 to 5.1)*	0.52
Fasting plasma insulin (pmol/l)	27.2	30.1	34.2	25.6* (7.2–49.2)	0.004	0.003	0.013	12.7 (−5.8 to 33.6)*	0.12
HOMA-IR	1.24	1.31	1.48	20.9* (5.1–39.1)	0.009	0.006	0.029	7.2 (−5.8 to 24.6)*	0.29
Maternal morbidity									
Obesity (BMI ≥25 kg/m^2)	30	34	58	2.43 (1.51–3.91)	0.001	0.001	0.001		
Central obesity (WHR >0.85)	9	16	19	1.81 (0.90–3.64)	0.098	0.11	0.12		
Adiposity (total body fat >35%)	52	62	76	1.78 (1.17–2.72)	0.007	0.01	0.032		
Q_4 HOMA-IR	28	36	46	1.68 (1.04–2.72)	0.04	0.051	0.16	1.12 (0.64–1.96)	0.71
IGT	16	13	16	1.08 (0.55–2.12)	0.83	0.95	0.92	0.78 (0.38–1.61)	0.52
Diabetes (known + new)	2 + 3	0 + 3	4 + 4	0.99 (0.34–2.91)	0.99, 0.18†	0.87	0.90	0.86 (0.28–2.65)	0.79
Plasma cholesterol >5.1 mmol/l	10	15	13	1.07 (0.51–2.24)	0.85	0.87	0.69	0.76 (0.34–1.70)	0.51
HDL cholesterol <1.0 mmol/l	69	64	70	0.85 (0.56–1.29)	0.46	0.43	0.56	0.94 (0.46–1.16)	0.18
Plasma triglycerides >1.7 mmol/l	10	10	19	2.28 (1.09–4.73)	0.027	0.04	0.029	2.17 (1.01–4.70)	0.05
Hypertension (known + new)	5 + 7	2 + 8	3 + 9	1.29 (0.58–2.83)	0.53	0.60	0.72	1.20 (0.44–2.34)	0.97
Metabolic syndrome	8	16	24	2.76 (1.40–5.40)	0.003	0.008	0.013	2.16 (0.99–4.69)	0.054

Anthropometric data are means, and glucose/insulin data are geometric means. The outcomes are change per 1-kg increase in offspring birth weight (percentage change for logged variables) and change in odds for maternal morbidity. †Significance for quadradic term. Metabolic syndrome based on World Health Organization 1999 criteria. Q_4, uppermost quartile.

(r = ~0.4, all $P < 0.001$), but relatively weakly related to head circumference ($r = 0.15$, $P < 0.01$) and not related to height ($r = 0.04$, $P = 0.33$). The prevalence of diabetes, hypertension, and hypertriglyceridemia was directly related to BMI (all $P < 0.001$). Higher SES was positively related to all anthropometric parameters in mothers ($P < 0.001$) and to plasma cholesterol concentration ($P < 0.05$), but not related to other cardiovascular risk factors. None of the mothers smoked or consumed alcohol.

Relations with offspring birth weight. There was a positive association between the birth weight of the child and maternal height, weight, BMI, obesity (BMI >25 kg/m^2), waist circumference, and fat mass 8 years later (Table 2). Offspring birth weight was not significantly

TABLE 3
Paternal size, glucose/insulin variables, and paternal morbidity measures 8 years after birth of the offspring according to sex-specific thirds of offspring birthweight

	Offspring birth weight tertile (sex-specific)			Adjusted for			
	1 (n = 132)	2 (n = 135)	3 (n = 128)	Paternal age, offspring sex	P	+SES (P)	+Paternal BMI (P)
Birth weight (kg)	2.26	2.74	3.28				
Anthropometry							
Height (cm)	164.6	165.9	167.7	2.89 (1.63–4.15)	0.001	0.001	
Weight (kg)	60.9	64.3	64.8	3.95 (1.63–6.27)	0.001	0.001	
BMI (kg/m^2)	22.6	23.3	23.0	0.60 (−0.17 to 1.38)	0.126	0.126	
Waist (cm)	83.9	87.3	86.5	2.55 (0.35–4.75)	0.023	0.034	
WHR	0.89	0.91	0.90	0.006 (−0.007 to 0.019)	0.39	0.51	
Fat mass (kg)	14.7	16.5	16.2	1.74 (0.55–2.93)	0.004	0.005	
Head circmference (cm)	54.8	54.9	55.1	0.37 (0.26–0.86)	0.049	0.057	
Glucose/insulin							
Fasting plasma glucose (mmol/l)	5.0	5.2	5.1	1.7* (−3.2 to 7.0)	0.50	0.71	0.89
2-h plasma glucose (OGTT) (mmol/l)	6.3	6.5	6.5	−0.5* (−8.3 to 8.0)	0.91	0.68	0.54
Fasting plasma insulin (pmol/l)	29.1	33.1	33.0	9.0* (−9.9 to 31.0)	0.34	0.38	0.68
30-min insulin increment	3.6	5.2	6.5	3.81 (−0.02 to 7.65)	0.051	0.055	0.048
Plasma split 32-33 insulin (pmol/l)	11.5	15.1	12.0	10.2* (−8.8 to 33.6)	0.31	0.25	0.48
Plasma proinsulin (pmol/l)	7.4	9.8	7.6	3.8* (−13.1 to 23.4)	0.68	0.57	0.97
HOMA-IR	1.73	2.18	1.90	9.4* (−8.6 to 32.3)	0.32	0.35	0.66
Glucose/insulin excluding IGT and diabetes							
Fasting plasma glucose (mmol/l)	4.8	4.9	4.8	0.7* (−3.4 to 5.1)	0.74	0.99	0.85
Fasting plasma insulin (pmol/l)	28.0	30.1	29.8	6.1* (−13.9 to 30.9)	0.58	0.52	0.69
HOMA-IR	1.54	1.79	1.55	4.7* (−13.9 to 27.1)	0.65	0.64	0.84
Paternal morbidity							
Obesity (BMI ≥25 kg/m^2)	31	40	37	1.45 (0.89–2.36)	0.13	0.16	
Central obesity (WHR >0.90)	68	85	71	1.38 (0.88–2.14)	0.16	0.27	
Adiposity (total body fat >25%)	61	76	67	1.45 (0.94–2.24)	0.095	0.12	
Q_4 HOMA-IR	23	41	29	1.25 (0.75–2.10)	0.39	0.44	0.74
IGT	16	25	22	1.17 (0.65–2.10)	0.59	0.74	0.86
Diabetic (known + new)	2 + 10	5 + 7	2 + 7	0.65 (0.29–1.47)	0.31	0.22	0.16
Plasma cholesterol >5.1 mmol/l	25	33	31	1.43 (0.85–2.40)	0.18	0.20	0.27
HDL cholesterol <0.9 mmol/l	62	69	59	1.07 (0.69–1.64)	0.77	0.50	0.64
Plasma triglycerides >1.7 mmol/l	37	42	39	1.37 (0.86–2.19)	0.19	0.31	0.44
Hypertension (known + new)	6 + 19	9 + 26	7 + 16	0.95 (0.56–1.62)	0.86	0.99	0.74
Metabolic syndrome	26	42	25	1.10 (0.66–1.82)	0.72	0.81	0.74

Anthropometric data are means, and glucose/insulin data are geometric means. The outcomes are change per 1-kg increase in offspring birth weight (percentage change for logged variables) and change in odds for paternal morbidity. Metabolic syndrome is based on World Health Organization 1999 criteria. Q_4, uppermost quartile.

related to maternal plasma glucose concentrations after fasting and after oral glucose load. The relative risk ratio for diabetes for mothers who gave birth to larger or smaller babies compared with those in the middle was not significant [2.61 (CI 0.71–9.80) and 1.68 (CI 0.41–6.89), respectively]; similarly, prevalence of IGT was not related to child's birth weight.

Maternal fasting plasma insulin concentration ($P < 0.01$) and HOMA-IR ($P < 0.01$) were directly related to offspring birth weight (adjusted for the child's sex and birth order and maternal age) (Table 2). This was true even when the analysis was limited to mothers with normal glucose tolerance ($P < 0.01$). These relationships remained significant after adjusting for socioeconomic status but became nonsignificant after adjusting for maternal BMI. Fasting plasma proinsulin and 32-33 split proinsulin concentrations and 30- and 120-min plasma insulin concentrations were not related to offspring birth weight. There was no significant relation between offspring birth weight and maternal blood pressure or plasma cholesterol concentrations (total, LDL, and HDL), but plasma triglyceride concentration was directly related ($P < 0.05$). Offspring birth weight was a strong predictor of metabolic syndrome in the mother ($P < 0.01$).

Fathers. Anthropometric measurements were available for 395 fathers and OGTT results for 398 fathers (Table 1). Altogether, 27% had BMI >25 kg/m^2, 57% had WHR >0.90, and 52% had body fat >25%. Plasma glucose and insulin (fasting and 30- and 120-min), HOMA-IR, triglyceride, and cholesterol concentrations were directly related ($P < 0.001$) and HDL cholesterol concentrations inversely related ($P < 0.05$) to BMI. The prevalence of diabetes, hypertension, and hypertriglyceridemia was directly related to BMI ($P < 0.001$). Higher SES was associated with larger size (height, BMI, waist circumference, and fat mass, all $P < 0.001$), higher plasma glucose (fasting and

120-min, $P < 0.05$), cholesterol and triglyceride concentrations (both $P < 0.01$), and diastolic blood pressure ($P < 0.05$).

Relations with offspring birth weight. Offspring birth weight was directly related to paternal height, weight, head and waist circumferences, and fat mass (Table 3). There were no significant relationships between offspring birth weight and paternal biochemical measurements (circulating glucose and insulin concentrations and HOMA-IR), blood pressure, or morbidity measures (Table 3). The birth weight of offspring of diabetic fathers (2.71 vs. 2.77 kg; $P = 0.50$), insulin-resistant fathers (2.81 vs. 2.76 kg; $P = 0.41$), or those with the metabolic syndrome (2.77 vs. 2.76 kg; $P = 0.84$) did not differ significantly from the remainder, even after excluding families with hyperglycemic mothers.

Adjusting for "assortive mating" and shared parental environment. Paternal and maternal height ($r = 0.29$, $P < 0.001$) and BMI ($r = 0.24$, $P < 0.001$) were significantly correlated. Paternal size was not related to maternal HOMA-IR after adjusting for maternal size. Maternal body size and HOMA-IR relations with offspring birth weight remained significant after adjusting for paternal height or BMI. After adjusting for maternal height or BMI, paternal height and weight, but not waist circumference or fat mass, remained significantly related to offspring birth weight. Adjustment for maternal BMI did not reveal any significant relationship between offspring birth weight and paternal metabolic-endocrine measures, including HOMA-IR.

DISCUSSION

Our study showed significantly increased obesity, insulin resistance, hypertriglyceridemia, and prevalence of metabolic syndrome in urban Indian mothers 8 years after the birth of heavier babies. There was no relation between offspring birth weight and maternal plasma glucose concentrations (fasting and post–glucose challenge) either including or excluding diabetic mothers. Our results suggest that the persistent metabolic abnormality in the urban Indian mothers 8 years after the birth of a heavier child is insulin resistance with compensated β-cell function rather than hyperglycemia. The mean birth weight of babies in the highest one-third was only 3.3 kg. These relationships were independent of the child's sex and maternal age, parity, and SES, but not maternal BMI, suggesting that determinants of body size (genetic, nutritional, and metabolic-endocrine) may be underlying factors. Obesity and insulin resistance are strong risk factors for diabetes and coronary heart disease (CHD). We therefore speculate that in the future there will be higher rates of diabetes and CHD in mothers of heavier babies. Though the child's birth weight was related to paternal size 8 years later, there were no relations with paternal glucose tolerance, insulin resistance, or other cardiovascular risk factors.

Mother-offspring relationships. Correlations between offspring birth weight and maternal size are expected. Mothers of heavy babies were fatter, taller, and had larger head circumference. This could reflect better nutrition and growth throughout life and/or genes for larger size. SES probably contributes to this relationship, although it remained significant after adjusting for SES.

It is general knowledge that mothers who give birth to heavy babies have an increased risk of diabetes, but there is little information on maternal risk of metabolic syndrome and cardiovascular risk. Serial studies of maternal metabolism before and during pregnancy have shown a relation between both pregestational ("chronic") and late gestational maternal insulin resistance and offspring birth weight (23) and with diabetes in the mother within 2 years of delivery (24,25). The increased size of the baby is thought to be due to maternal hyperglycemia during pregnancy causing fetal hyperinsulinemia and promoting insulin-mediated growth (26). In our study, offspring birth weight predicted maternal insulin resistance 8 years after delivery, which was independent of age, parity, and SES and was also present in the normal glucose-tolerant mothers (at the time of testing, excluding those with a history of GDM). There was no relationship between offspring birth weight and maternal glycemia 8 years after delivery. One interpretation of our findings is that insulin resistance may be on the causal pathway in the maternal-offspring size relationship. The likely sequence of events is that mothers of heavier babies were more obese at the time of pregnancy (and therefore more insulin resistant) and remained so 8 years later. Our findings indirectly support the possibility that maternal circulating nonglucose nutrients (amino acids, triglycerides, fatty acids, etc.) may be important determinants of fetal size (27) and that maternal insulin resistance helps facilitate transfer to the fetus. Our data are consistent with the concept that maternal size and metabolic status, even in the absence of gestational diabetes, may have a major influence on offspring size at birth.

An alternative explanation for the birth weight–insulin resistance relationship would be "reverse causality." A large fetus may promote increased maternal insulin resistance through the secretion of larger quantities of placental hormones (lactogen, growth hormone, etc.) (28). This could occur if the fetus is "genetically" large (paternal influence). However, we did not find a relation between paternal height or BMI and maternal HOMA-IR, independent of maternal size. A reverse causality explanation could hasten maternal β-cell decompensation, and thus later diabetes, but does not readily explain either persistent obesity or insulin resistance in the mother 8 years after delivery.

Our findings are different from those reported by Lawlor et al. (9), who found an inverse relation between offspring birth weight and maternal HOMA-IR in elderly British women (69 years of age). There may be a number of explanations for this difference. Causes of low birth weight may be different in the two populations; in developed countries, these include prematurity, pregnancy-induced hypertension, and maternal smoking, which would increase the risk of future cardiovascular disease in the mother (29,30). On the other hand, low birth weight in India is related to the small size of mothers and poor nutrition (31–33), which would protect against obesity, insulin resistance, and CHD. Also, Indian babies (34,35) and adults (36,37) have a higher percentage body fat for a given BMI compared with Caucasians. This may alter the relation between body size and disease risk in Indians compared with Caucasians (38,39). The relation between

offspring birth weight and maternal insulin resistance may change with time from delivery (9,10), although "survivor bias" may contribute to the changing relationship. For example, insulin-resistant and obese mothers with polycystic ovarian disease will be selectively excluded from a retrospective cross-sectional cohort because of infertility or early pregnancy loss or because of premature death due to diabetes or heart disease (40). Finally, the differences in the socioeconomic and nutritional transition may explain the difference: in Europe, obesity, diabetes, and CHD are more common in the lower social classes who have lower–birth weight babies, but in India, these conditions are more common in the affluent, who produce heavier babies.

Father-offspring relationships. The independent relation between paternal height and offspring birth weight is consistent with the idea that the paternal genome has a strong influence on fetal skeletal growth (41); however, other size relationships (measures of obesity) may reflect an "assortive mating" effect because they did not remain significant after adjusting for maternal size. Lack of relation between offspring birth weight and paternal insulin resistance or glucose tolerance is unlike the findings in Pima Indians (42) and in the U.K. (10), both of which showed an inverse relationship. Thus, our data does not support the paternal predictions of fetal insulin hypothesis (5). This may be partly due to lower prevalence of diabetes in our population than among the Pima Indians. However, in a rural Indian population, paternal insulin resistance was directly related to offspring birth weight, a relationship that was dependent on paternal BMI (43,44). Paternal genetic influences may control fetal size rather than metabolism.

Barker (1) has proposed that the risk of diabetes and CHD will diminish over time as maternal nutrition, and thus fetal growth, improves. CHD has shown a downward trend in some Western countries (at least partly contributed to by improved lifestyle) but not diabetes. "Improvements" in the nutritional status of Indian mothers that simply increase their adiposity may increase fetal size and improve perinatal outcomes, but could carry a price in terms of an increased risk of diabetes and the metabolic syndrome in both mother and offspring. The higher incidence of diabetes and CHD in urban compared with rural India may reflect such a mechanism. The important issues of maternal insulin resistance during pregnancy, fetal growth, and future risk of diabetes and CHD in both mother and child need to be further investigated in prospective multiethnic studies. What constitutes improved nutrition for women before and during pregnancy also needs to be more clearly understood.

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