Insulin Resistance Syndrome in 8-Year-Old Indian Children

Small at Birth, Big at 8 Years, or Both?

Ashish Bavdekar, Chittaranjan S. Yajnik, Caroline H.D. Fall, Swatee Bapat, Anand N. Pandit, Vaishali Deshpande, Sheila Bhave, Sam D. Kellingray, and Charu Joglekar

We have studied 477 8-year-old Indian children to define the relationship between birth weight and cardiovascular risk factors, including insulin resistance syndrome (IRS) variables and plasma total and LDL cholesterol concentrations. All risk factors were strongly related to current weight. After adjustment for current weight, age, and sex, lower birth weight was associated with higher systolic blood pressure (P = 0.008), fasting plasma insulin and 32–33 split proinsulin concentrations (P = 0.08 and 0.02), glucose and insulin concentrations 30 min postglucose (P = 0.06 and 0.04), subscapular/triceps skinfold ratio (P = 0.003), and plasma total and LDL cholesterol concentrations (P = 0.002 and 0.001). Lower birth weight was associated with increased calculated insulin resistance (homeostasis model assessment [HOMA], P = 0.03), but was not related to the HOMA index of β-cell function. The highest levels of IRS variables and total and LDL cholesterol were in children of low birth weight but high fat mass at 8 years. Taller height at 8 years predicted higher fasting plasma insulin concentrations, insulin resistance, and plasma total and LDL cholesterol concentrations. The most insulin-resistant children were those who had short parents but had themselves grown tall. Although the implications of our findings in relation to height are unclear, interventions to improve fetal growth and to control obesity in childhood are likely to be important factors in the prevention of cardiovascular disease and IRS in India. ***Diabetes*** **48:2422–2429, 1999**

India is experiencing an "epidemic" of type 2 diabetes and coronary heart disease (CHD) among its young adult and middle-aged population (1–4). Indians as a race are characteristically more insulin resistant than white Caucasians and express the insulin resistance syndrome (IRS) (metabolic syndrome or syndrome X: insulin resistance, hypertension, glucose intolerance, hypertriglyceridemia, and low serum HDL cholesterol concentrations) in an exaggerated manner (5–7). This occurs even in the absence of generalized obesity, possibly because these subjects are centrally obese (8). A traditional explanation has been that Indians have enriched a thrifty genotype that has become detrimental in a modern urban setting (8,9). Recent research in the U.K., Europe, and the U.S. has shown that insulin resistance is increased in men and women who had a low birth weight (10–12). This finding has led to an alternative (thrifty phenotype) hypothesis, which proposes that IRS results from persistence of fetal adaptations to inadequate intrauterine nutrition (13). If this is correct, India's high rates of type 2 diabetes and CHD may be a consequence of poor fetal growth; the mean birth weight in India is 2.6–2.7 kg, one of the lowest in the world (14,15).

In 1995, we reported in 4-year-old Indian children that lower birth weight was associated with higher glucose and insulin concentrations 30 min after an oral glucose load (16). We suggested that this may be early evidence of insulin resistance. We have now restudied these children at the age of 8 years and selected additional children from the King Edward Memorial Hospital (KEMH) obstetric records, especially at the extremes of birth weight.

RESEARCH DESIGN AND METHODS

Sample selection. We aimed to study children born in the KEMH as full-term singleton deliveries (born at ≥37 weeks' gestation based on the mother's last menstrual period date) and now aged 8.00–8.99 years. Our sampling frame comprised *1*) children who had taken part in the earlier study at the age of 4 years, and *2*) additional children selected from the labor ward registers. The former group were 201 children born in KEMH during October 1987 to April 1989, weighing >2,000 g at term and admitted to the routine postnatal wards. Of these, 190 (95%) were successfully retraced and included in the current study. Additional children (the second group) were selected from all full-term singleton live births in KEMH during July 1987 to June 1989. Based on a statistical power calculation, we aimed for a final sample of 500 children with equal numbers (n = 63) in each of eight birthweight groups representing 250-g increments. Where excess babies were listed, the required number was selected using random number tables. The sample is shown in full in Table 1. Of the 518 children selected, 166 had moved away from

From the Department of Pediatrics (A.B., S.Ba., A.N.P., S.Bh.) and the Diabetes Unit (C.S.Y., V.D., C.J.), King Edward Memorial Hospital, Pune, Maharashtra, India; and the Medical Research Council Environmental Epidemiology Unit (C.H.D.F., S.D.K.), University of Southampton, Southampton General Hospital, Southampton, U.K.

Address correspondence and reprint requests to Dr. C.S. Yajnik, Diabetes Unit, King Edward Memorial Hospital, Rasta Peth, Pune, Maharashtra, India 411011. E-mail: diabetes@vsnl.com.

Received for publication 30 March 1999 and accepted in revised form 27 August 1999.

CHD, coronary heart disease; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; KEMH, King Edward Memorial Hospital; MPH, mid-parental height; SS/TR, subscapular-to-triceps skinfold ratio.

TABLE 1
Study sample selection

Birth weight (g)	Children studied at 4 years (x)	Additional children required ($63x$)	Additional children to be selected from labor ward register ($63x \times 3$)	Singleton term births in KEMH listed in the labor ward register	Additional children selected	Numbers in current study		
						Original 4-year study children	New children	Total
≤1,750	0	63	189	12	12 (All)	0	4	4
≤2,000	0	63	189	35	35 (All)	0	18	18
≤2,250	13	50	150	108	108 (All)	12	43	55
≤2,500	44	19	57	244	57	43	45	88
≤2,750	44	19	57	411	57	41	37	78
≤3,000	57	6	21	523	21	54	33	87
≤3,250	27	36	108	273	108	24	52	76
>3,250	16	47	141	250	141	16	55	71
Total	201	304	912	1,856	518	190	287	477

Data are n unless otherwise indicated.

the address listed in the obstetric records and could not be traced, 60 declined to take part in the study, and 287 (55%) agreed to take part. The total number studied was therefore 477.

Procedures. The children stayed overnight with their parents in the KEMH Diabetes Research Unit. In the morning, fasting blood samples were taken for measurement of plasma lipids (total cholesterol, HDL cholesterol, and triglycerides) and plasma glucose, insulin, proinsulin, and 32–33 split proinsulin. Further blood samples were taken 30 and 120 min after a 1.75 g/kg body weight oral glucose for measurement of plasma glucose and insulin concentrations. Systolic and diastolic blood pressures were measured following the 30-min blood sample, after 5 min resting quietly, using a digital automated device (Dinamap; Criticon, Tampa, FL) and a cuff of the appropriate size for the measured arm circumference.

Anthropometry was measured by one of two observers. Weight was measured to the nearest 0.5 kg using a portable Seca scale; height to the nearest 0.5 cm using a wall-mounted stadiometer; waist circumference to the nearest 0.1 cm, midway between the lower costal margin and the superior iliac crest, in expiration, with the child supine; and hip circumference to the nearest 0.1 cm, with the child standing, as the largest measured circumference at the approximate level of the greater femoral trochanters. Triceps and subscapular skinfolds were measured to the nearest 0.2 mm using Harpenden calipers (CMS Instruments, London). Parental weights and heights were also measured. Socioeconomic status was assessed using the Kuppuswamy score, a standardized scoring system based on a questionnaire administered to the parents, asking for details of education, income, and type of housing (17). Before starting the study, anthropometric techniques were standardized. Ethical permission was obtained from the KEMH Ethics Committee, and parental consent was obtained.

Laboratory methods. Plasma glucose and serum cholesterol, HDL cholesterol, and triglyceride concentrations were measured in Pune, India, using standard enzymatic methods (Spectrum; Abbott, Irving, TX). Between-batch coefficients of variation for all the assays were <3% in the normal range. LDL cholesterol was calculated using the Friedewald-Fredrickson formula (18). Plasma insulin, proinsulin, and 32–33 split proinsulin concentrations were measured in Cambridge, England, U.K. Insulin was measured using a two-site immunoenzymometric assay (Medgenix, Fleurus, Belgium), which did not cross-react with intact or 32–33 split proinsulin. Between-batch coefficients of variation were 11% at 24 pmol/l, 8% at 60 pmol/l, and 4.8% at 477 pmol/l. A two-site immunometric assay was used to measure 32–33 split proinsulin (19,20). Intact proinsulin was measured using a microtitre plate time-resolved fluorescence (delfia) assay. The solid-phase and labeled antibodies used were the same monoclonal antibodies described for the immunoradiometric assay of intact proinsulin (19,20). Tracer antibody was labeled with Europium using the Delfia Europium labelling kit 1244–302 (Wallac, Milton Keynes, Bucks, U.K.). This assay did not cross-react with insulin and 32–33 split proinsulin. Between-batch coefficients of variation were 10% at 4.4 pmol/l, 5.8% at 24 pmol/l, and 5.4% at 86 pmol/l.

Statistical methods. To satisfy assumptions of normality, measurements of BMI, mid-upper-arm, waist, and hip circumferences and skinfold thickness required reciprocal transformation, and measurements of subscapular-to-triceps skinfold ratio (SS/TR), systolic and diastolic blood pressures, plasma insulin, proinsulin, 32–33 split proinsulin, and total, LDL, and HDL cholesterol and triglyceride concentrations were log-transformed. Comparisons between the sexes were made using t tests. Adjustments of cardiovascular risk variables for sex, age, and body weight, and analysis of their relationships to birth weight, were made using multiple linear regression. Fat mass was calculated using the formula: (0.23 × subscapular skinfold thickness) + (0.18 × weight) + (0.13 × triceps skinfold thickness) − 3.0 (21). Estimates of pancreatic β-cell function and relative insulin resistance were determined using HOMA equations (22). We have used the 30-min insulin increment (23,24) as an additional estimate of β-cell function.

RESULTS

The children's ages ranged from 8.05 to 8.87 years (mean ± SD 8.47 ± 0.11). Table 2 shows their mean birth weight and current (8-year) anthropometry, blood pressure, and biochemical measurements. Seven children had impaired glucose tolerance (IGT) (World Health Organization definition [25]), but none were diabetic.

Sex, current body size, and social class. Boys had a higher mean birth weight and larger head circumference at 8 years, but thinner skinfolds and lower fat mass than girls (Table 2). There were no significant differences between the sexes in 8-year weight, height, measures of central fat (waist/hip or SS/TR ratios), blood pressure, or plasma lipid concentrations. Girls had higher insulin, proinsulin, and 32–33 split proinsulin concentrations than boys. Birth weight was only marginally higher in children of higher social class ($P = 0.4$), but 8-year measurements, including weight, height, BMI, and fat mass, rose markedly with increasing social class ($P < 0.001$ for all).

Many of the outcome variables were higher in children of higher current body weight. This was true of systolic blood pressure ($P < 0.05$), plasma insulin (fasting and postload), proinsulin and 32–33 split proinsulin concentrations, relative insulin resistance (HOMA) and β-cell function (HOMA), 30-min insulin increment and fasting plasma total, and LDL cholesterol and triglyceride concentrations ($P \leq 0.001$ for all). These results partly reflected an association with body fat; they were all correlated with skinfold measurements and generally more strongly with subscapular ($P \leq 0.01$ for all) than with triceps skinfold thickness. Insulin and total and LDL cholesterol also showed a relationship with height. Plasma insulin (fasting and postload), fasting proinsulin and 32–33 split proinsulin concentrations, and insulin resistance (HOMA), were higher in taller children ($P < 0.01$ for all), as were plasma total ($P < 0.01$) and LDL cholesterol concentrations ($P = 0.02$).

TABLE 2
Mean birth weight and anthropometric measurements, blood pressure, and circulating biochemical parameters at age 8 years

	Girls	Boys
n	221	256
Birth weight (kg)	2.7 ± 0.5	2.8 ± 0.5*
8-Year results		
Height (cm)	124.7 ± 6.3	125.4 ± 5.9
Weight (kg)	21.3 ± 4.1	22.0 ± 4.0
BMI (kg/m^2)	13.4 (12.4–14.2)	13.7 (12.8–14.6)*
Head circumference (cm)	49.9 ± 1.5	50.4 ± 1.6*
Mid-upper arm circumference (cm)	16.3 (15.3–17.2)	16.2 (15.2–17.1)
Waist/hip ratio (%)	82.7 ± 5.1	82.8 ± 5.1
Triceps skinfold (mm)	8.1 (6.9–10.1)	6.7 (5.8–8.1)†
Subscapular skinfold (mm)	6.5 (5.5–7.8)	5.5 (4.7–6.5)†
SS/TR	0.8 (0.7–0.9)	0.8 (0.7–0.9)
Fat mass (kg)	3.7 ± 1.8	3.3 ± 1.5*
Blood pressure (mmHg)		
Systolic	111.2 (105.0–118.0)	111.4 (106.0–117.0)
Diastolic	62.7 (57.5–69.0)	62.9 (58.0–68.0)
Glucose (mmol/l)		
Fasting	4.5 ± 0.6	4.6 ± 0.8
30-min	7.6 ± 2.0	7.3 ± 1.4*
120-min	5.3 ± 1.2	5.1 ± 1.0
Insulin (pmol/l)		
Fasting	25.3 (19.0–35.0)	23.2 (16.0–35.0)
Proinsulin (fasting)	3.4 (2.6–4.5)	3.1 (2.3–4.2)*
32–33 split proinsulin (fasting)	4.8 (3.3–6.8)	3.7 (2.6–5.3)†
30-min	177.5 (119.0–295.8)	158.2 (97.0–272.0)
120-min	92.8 (53.8–169.3)	72.6 (44.3–121.0)*
Cholesterol (mmol/l)		
Total	3.4 (3.1–3.8)	3.4 (3.0–3.8)
LDL	2.0 ± 0.6	2.0 ± 0.6
HDL	1.0 (0.9–1.3)	1.1 (0.9–1.3)
Triglycerides (mmol/l)	0.7 (0.6–0.9)	0.7 (0.5–0.9)

Data are *n* or means ± SD, except for BMI, mid-upper arm circumference, triceps skinfold, and subscapular skinfold, which are harmonic mean (interquartile range), and data for SS/TR, blood pressure, insulin, proinsulin, split proinsulin, cholesterol, and triglycerides, which are geometric mean (interquartile range). *P* for difference between sexes:*$P < 0.05$, †$P < 0.0001$.

SS/TR and waist/hip ratios were higher in children with fatter skinfolds (SS/TR: $P < 0.001$ for subscapular, $P = 0.003$ for triceps; waist/hip: $P < 0.01$ for subscapular, $P = 0.04$ for triceps).

In order to assess "clustering" of the different components of the IRS in our children, we designated a child positive for an IRS variable if his or her value was above the highest quartile for insulin resistance (HOMA), systolic blood pressure, or plasma triglyceride concentration, or below the lowest quartile for plasma HDL cholesterol concentration. We started with 109 children who were above the highest quartile for insulin resistance (HOMA). Of these, 55 children were positive for insulin resistance (HOMA) alone without any other features of the IRS (group 1), 30 for insulin resistance plus any one of the other main IRS variables (systolic blood pressure, plasma triglyceride, and HDL cholesterol concentrations) (group 2), 21 for insulin resistance plus two IRS variables (group 3), and 3 for insulin resistance plus all three other variables (group 4). Current weight, height, and fat mass increased from group 1 to group 4 ($P < 0.001$, for all), indicating a strong association between increasing body size and clustering of the features of the IRS.

Relationships with birth weight. Children of higher birth weight were heavier and taller at 8 years (Table 3) and tended to have fatter triceps and subscapular skinfold thicknesses ($P = 0.007$ and $P = 0.1$, respectively, adjusted for age and sex). Table 3 also shows mean values for all cardiovascular risk variables according to birth weight. Systolic blood pressure, plasma LDL cholesterol concentrations, and SS/TR ratios were inversely related to birth weight. These relationships were stronger after adjustment for age, sex, and current body weight; inverse trends were then also seen with fasting plasma insulin and 32–33 split proinsulin concentrations, insulin resistance (HOMA), 30-min plasma glucose and insulin concentrations, and plasma total cholesterol concentrations. After adjustment for current weight, lower birth weight was also associated with increased clustering of the IRS variables ($P < 0.001$). All these trends remained significant after further adjustment for social class, except for fasting insulin ($P = 0.1$) and 30-min glucose ($P = 0.07$). Although plasma triglyceride concentrations tended to fall and HDL cholesterol concentrations to rise with increasing birth weight, these trends were not statistically significant. There were no relationships between birth weight and diastolic blood pressure, fasting and 120-min glucose concentrations, β-cell function (HOMA and 30-min insulin increment), or waist/hip ratio (Table 3). There was no significant difference in birth weight between the seven children with IGT (2.9 kg) and those with normal glucose tolerance.

TABLE 3
Mean height, weight, blood pressure, plasma glucose, insulin, and lipid concentrations, and measures of central fat, according to birth weight

	Birth weight (kg)								
	≤2.0	≤2.25	≤2.5	≤2.75	≤3.0	≤3.25	>3.25	*P*	Adjusted *P*
Weight (kg)	20.8	19.7	21.1	21.4	21.7	22.2	23.6	<0.001	—
Height (cm)	123.3	121.6	124.3	124.6	125.6	126.3	127.9	<0.001	—
BMI (kg/m^2)	13.5	13.1	13.4	13.5	13.6	13.7	14.1	<0.001	—
Blood pressure (mmHg)									
Systolic	115.7	111.1	112.3	109.1	112.1	111.8	109.8	0.06	0.008
Diastolic	66.0	61.5	62.7	62.2	63.8	62.9	62.4	0.7	0.7
Glucose (mmol/l)									
Fasting	4.8	4.6	4.5	4.7	4.5	4.5	4.6	0.97	0.6
30-min	7.3	7.9	7.6	7.4	7.3	7.0	7.4	0.07	0.06
120-min	5.4	5.4	5.1	5.3	5.2	5.1	5.2	0.6	0.8
Insulin (pmol/l)									
Fasting	31.9	22.6	23.7	24.3	23.7	22.5	26.1	0.7	0.08
Proinsulin	3.6	3.1	3.2	3.5	3.2	3.2	3.3	0.8	0.1
32–33 split proinsulin	5.4	3.9	4.0	4.6	4.3	3.9	4.0	0.3	0.02
30-min	166.5	180.4	170.3	160.1	158.6	158.9	178.6	0.7	0.04
120-min	108.0	83.8	73.0	84.3	80.6	80.0	81.7	0.4	0.1
30-min insulin increment	16.7	20.7	19.8	16.0	17.9	18.5	20.9	0.9	0.2
β-cell function (HOMA)	126.6	93.4	111.4	105.0	108.1	100.8	98.6	0.3	0.1
Insulin resistance (HOMA)	1.3	0.9	0.9	1.0	1.0	0.9	1.0	0.6	0.03
Cholesterol (mmol/l)									
Total	3.5	3.4	3.5	3.4	3.5	3.2	3.4	0.1	0.002
LDL	2.1	2.1	2.1	2.0	2.1	1.8	1.9	0.03	0.001
HDL	1.1	1.0	1.0	1.1	1.0	1.1	1.1	0.1	0.2
Triglycerides (mmol/l)	0.8	0.6	0.8	0.8	0.7	0.7	0.7	0.5	0.2
Waist/hip ratio	84.8	82.2	83.0	82.7	82.7	81.4	83.6	0.3	0.4
SS/TR	88.3	83.7	84.1	80.4	81.6	77.7	82.2	0.05	0.003

P values are derived by multiple linear regression using variables as continuous. Adjusted *P* values are adjusted for age, sex, and current body weight.

Interactions between birth weight and current weight. Figure 1 shows insulin resistance (HOMA), systolic blood pressure, SS/TR, and plasma total cholesterol concentrations in relation to birth weight and current weight simultaneously. The inverse trends with birth weight were strongest in the highest 8-year weight group. The positive trends with current weight tended to be strongest in the lowest birth-weight group. The highest values were seen in children who were light at birth and heavy at 8 years. Though not shown in the figure, results were similar for plasma triglyceride concentration. The interaction term (birth weight × current weight) was statistically significant for insulin resistance ($P = 0.004$), but not for systolic blood pressure ($P = 0.4$), plasma triglyceride concentrations ($P = 0.3$), SS/TR ratio ($P = 0.5$), or plasma total cholesterol concentrations ($P = 0.8$; all adjusted for age and sex).

To determine how different components of 8-year body weight were related to IRS variables, multiple regression analyses were carried out, including current fat mass and height instead of overall weight (Table 4). Higher fat mass was strongly associated with increased insulin resistance, systolic blood pressure, plasma triglyceride concentrations, SS/TR ratio, and plasma total cholesterol concentration. Taller height was associated with increased insulin resistance, but was not related to the other outcomes. Birth weight was inversely related to all outcomes except plasma triglyceride concentration.

We repeated all these analyses, limiting the sample to the 190 children who took part in our earlier study at age 4 years. In this smaller group of children, none of the outcome variables was significantly related to birth weight. The B values for the change in the major IRS variables (insulin resistance, systolic blood pressure, plasma triglyceride concentration, SS/TR, and plasma cholesterol concentration) were as follows: logged insulin resistance –4.9%; logged systolic blood pressure –0.6%; logged triglyceride concentration –7.4%; logged SS/TR –2.0%; and logged cholesterol –4.7%. These are all within the 95% CIs for the sample as a whole (Table 5).

Parental height. Finally, we examined the relationship of the IRS variables to maternal and paternal heights and mid-parental height (MPH), which is used clinically as an indicator of "genetic" growth potential (boys: [(maternal height + paternal height in centimeters)/2] + 7 cm; girls: [(maternal height + paternal height in centimeters)/2] – 7 cm (26). Insulin resistance (HOMA), but not the other IRS variables, was inversely related to MPH ($P < 0.001$), independently of the child's own birth weight and current height, weight, and fat mass. The most insulin-resistant children were those whose parents were short, but who had grown tallest at 8 years. Maternal and paternal heights contributed independently to this effect, both being significantly related to insulin resistance when added to the regression analysis in place of MPH. When MPH, or maternal and paternal heights, were added to the regression shown in Table 4, the relationship of insulin

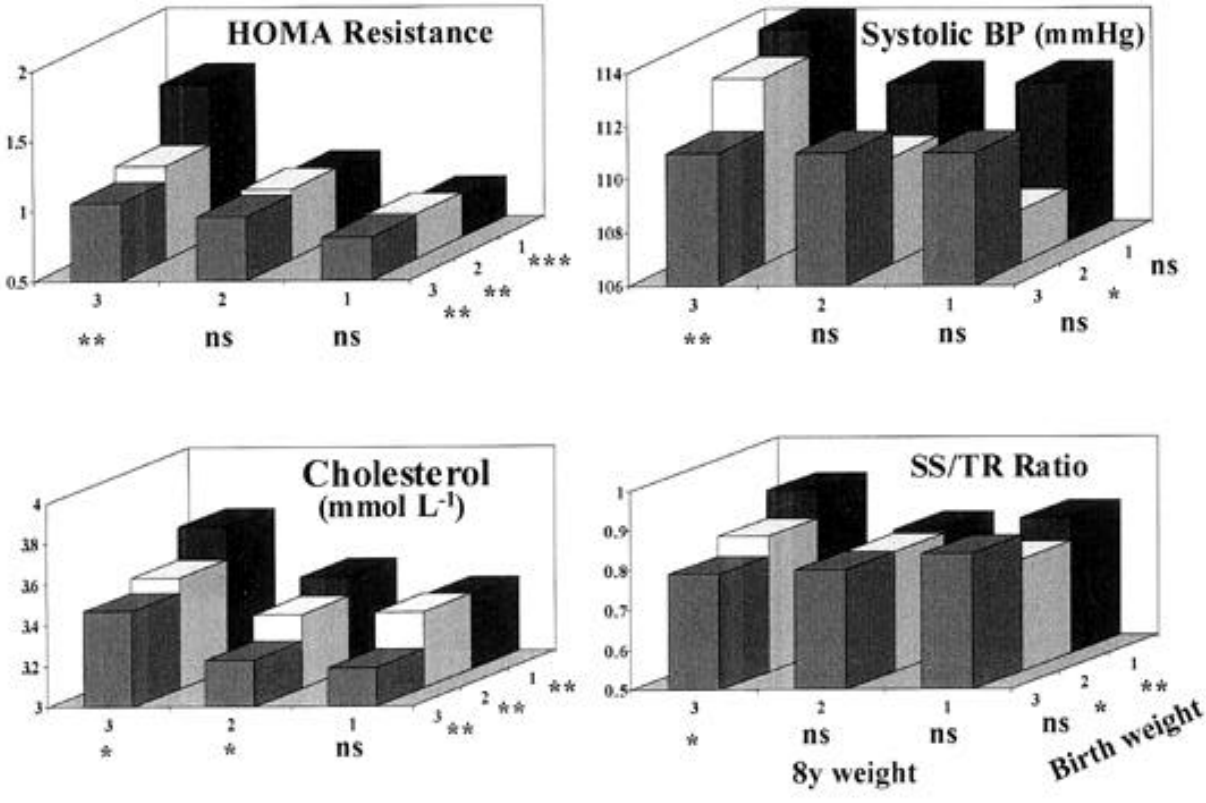

FIG. 1. Mean levels of insulin resistance variable (HOMA), systolic blood pressure, serum cholesterol concentration, and SS/TR at 8 years of age by tertiles of birth weight and 8-year weight. Significance level for the trend in each row and column (adjusted for age and sex) is shown at the end. ns, not significant, *P < 0.05, **P < 0.01, ***P < 0.001.

resistance to the child's 8-year height remained strongly statistically significant, while that to birth weight was no longer significant (Table 5). The other IRS variables and total and LDL cholesterol concentrations were unrelated to parental height, and remained significantly related to birth weight when parental heights were added to the regressions shown in Table 4.

DISCUSSION

We have measured cardiovascular disease risk factors, including components of the insulin resistance syndrome, and plasma total and LDL cholesterol concentrations, in a large sample of healthy 8-year-old Indian children (Table 2). Children who were heavier at 8 years had higher plasma insulin and proinsulin concentrations, calculated insulin resistance (HOMA), systolic blood pressures, SS/TR skinfold thickness ratios, and plasma total and LDL cholesterol concentrations. After adjustment for current weight, all these risk factors were higher in children of lower birth weight (Table 3).

Our findings for insulin resistance and the IRS variables are similar to those in 10-year-old children in the U.K. (27), and in adults in the U.K. (10), Europe (11), and India (28). Consistently with other studies (29,30), we found no association between birth weight and insulin secretion. Several groups (12,31–33) have reported no association between birth weight and circulating total or LDL cholesterol in later life. A study in the U.K., however, showed an inverse relationship with abdominal circumference at birth, thought to reflect neonatal liver size (34). The association of low birth weight with high plasma LDL cholesterol concentration in our children may reflect the smaller abdominal circumference (and presumably liver growth) of Indian babies (35). While cardiovascular risk variables were more strongly related to current weight than to birth weight, our results support the hypothesis that reduced fetal growth, or the factors that cause it, has lasting endocrine and metabolic effects culminating in the later development of the IRS and cardiovascular disease (13,36). Fetal growth is thought to be strongly influenced by environmental factors, such as maternal size and nutrition, and infections (37). Genetic factors certainly contribute to fetal growth, although so far few specific genes have been identified (38). Our data suggest that interventions to prevent the IRS and cardiovascular disease should include measures to improve fetal growth in India, where approximately one-third of newborn babies weigh ≤2.5 kg at birth (15).

Children with the most adverse cardiovascular risk profiles (including clustering of the IRS variables) were light at birth and heavy at 8 years. Risk variables were related to birth weight only in heavier children, and to current weight most strongly in children of low birth weight (Fig. 1). A similar pattern has been shown in two other recent studies of children, from the U.K. (27) and South Africa (39). Of the components of body weight, higher fat mass was associated with an increase in all the risk variables. We speculate that reduced intrauterine growth induces endocrine and metabolic adaptations to allow the best use of available nutrients for survival in utero. These adaptations may limit options for nutrient utilization in later life, and in situations of positive energy balance lead to excess fat deposition, especially in central depots, which aggravates insulin resistance. This hypothesis

TABLE 4
Multiple regression analysis of IRS variables with current (8-year) height and fat mass, birth weight, age, and sex

	B (95% CI)	*P*
Log insulin resistance (HOMA)		
Height (cm)	1.6 (0.6 to 2.6)	<0.001
Fat mass (kg)	8.3 (4.9 to 11.9)	<0.001
Birth weight (kg)	–9.7 (–18.6 to 0.2)	0.05
Age (years)	50.2 (–3.4 to 133.7)	0.07
Sex (boys, 1; girls, 2)	7.6 (–2.3 to 18.4)	0.1
Log systolic blood pressure (mmHg)		
Height (cm)	0.008 (–0.2 to 0.2)	0.9
Fat mass (kg)	0.7 (0.1 to 1.3)	0.01
Birth weight (kg)	–1.8 (–3.5 to 0.0)	0.04
Age (years)	7.9 (0.2 to 16.2)	0.04
Sex	–0.5 (–2.1 to 1.1)	0.5
Log plasma triglycerides (mmol/l)		
Height (cm)	–0.3 (–1.1 to 0.5)	0.4
Fat mass (kg)	5.0 (2.1 to 8.0)	<0.001
Birth weight (kg)	–4.1 (–12.2 to 4.7)	0.3
Age (years)	–18.5 (–43.8 to 18.3)	0.3
Sex	2.1 (–5.7 to 10.6)	0.6
Log SS/TR		
Height (cm)	–0.3 (–0.7 to 0.1)	0.09
Fat mass (kg)	3.9 (2.4 to 5.3)	<0.001
Birth weight (kg)	–4.8 (–8.7 to –0.7)	0.02
Age (years)	–5.5 (–20.9 to 12.9)	0.5
Sex	–3.5 (–7.1 to 0.2)	0.06
Plasma total cholesterol concentration (mmol/l)		
Height (cm)	0.3 (–0.1 to 0.7)	0.07
Fat mass (kg)	2.0 (0.8 to 3.3)	<0.001
Birth weight (kg)	–5.3 (–8.6 to –1.2)	0.003
Age (years)	0.7 (–13.7 to 17.5)	0.9
Sex	–1.7 (–5.0 to 1.7)	0.3

B values are percentage changes in the outcome variable per unit change in predictor variables.

TABLE 5
Multiple regression analysis of insulin resistance with current (8-year) height and fat mass, birth weight, age, and sex, and parental heights

	B (95% CI)	*P*
Log insulin resistance (HOMA)		
Height (cm)	2.7 (1.5 to 3.3)	<0.001
Fat mass (kg)	6.7 (2.7 to 10.8)	<0.001
Birth weight (kg)	–1.4 (–12.4 to 11.0)	0.8
Age (years)	–32.3 (–58.9 to 11.6)	0.1
Sex (boys, 1; girls, 2)	9.2 (–1.8 to 21.4)	0.1
Father's height (cm)	–1.2 (–2.1 to –0.2)	0.01
Mother's height (cm)	–1.1 (–2.1 to –0.1)	0.04

B values are percentage changes in the outcome variable per unit change in predictor variables.

is supported by studies showing that lower birth weight predicts higher waist/hip ratio in adults (40) and SS/TR ratio in adults (12) and children (41,42). Our observation that lower birth weight predicts higher SS/TR ratio, a better indicator of central fatness in children than waist/hip ratio (43), in prepubertal children from a developing country highlights the importance of poor intrauterine growth in relation to later central obesity. Excess fat tissue could lead to the IRS either by overproduction of nonesterified fatty acids and the glucose–fatty acid cycle (44), or through increased synthesis and release of leptin (45) or proinflammatory cytokines (46).

Children who were light at birth and tall at 8 years had increased insulin resistance (Table 4). It is possible that a low-birth-weight baby who grows tall postnatally has experienced greater intrauterine growth retardation relative to its growth potential than one who does not (47,48). Thus it may be the postnatal "catch-up" growth, and/or the intrauterine growth retardation which preceded it, that is associated with increased insulin resistance. Another possibility is that taller height at 8 years reflects advanced skeletal maturity. Lower birth weight has been associated with earlier menarche (49) and possibly adrenarche (50). In this case, we might expect insulin resistance to be associated with reduced final (adult) height in these children.

One of our new findings was that short maternal and paternal height independently predicted insulin resistance in the children. The most insulin-resistant children were those whose parents were short but who had grown tall at 8 years. After adjusting for parental height, insulin resistance was still related to 8-year height but was no longer related to birth weight. In a well-nourished population, parental heights reflect genetic height potential (51). Our findings may therefore reflect a genetic mechanism. For example, since insulin is a growth factor in utero and postnatally, genetically mediated insulin resistance could be associated with short parental stature and low birth weight in the offspring (52). It is difficult in that case, however, to explain the childrens' greater height at 8 years. Alternatively, our results may have an intrafamilial environmental explanation. In our population, short stature in the parents could reflect poor nutrition during their own childhood and adolescence (51).

The apparently stronger relationships of risk variables to birth weight in this study than in our earlier 4-year study may indicate that the relationships strengthen with age, as has been suggested for blood pressure (53). In view of the negative findings when we limited the analysis to the 190 children who took part previously, however, a more likely explanation is that the higher numbers of children in the current study, especially at the extremes of birth weight, simply increased the statistical power.

In summary, we have shown that after adjustment for current weight, IRS variables and plasma total and LDL cholesterol concentrations at 8 years are inversely related to birth weight. Children with the most adverse risk profiles are those who were born small but who are relatively fat and tall at 8 years. While we are unsure how to interpret our findings in relation to tall height, our results indicate that a high fat mass is particularly detrimental, in terms of cardiovascular risk, in low-birth-weight children. This is supported by a recent study in Finland showing that men who were thin at birth but fat in childhood had increased coronary heart disease mortality (54). Increasing body fat and height are well-known secular trends in socioeconomically developing communities (51,55). High cardiovascular risk in low-birth-weight individuals may therefore be an inevitable consequence of such development. In the long term, improvement in fetal growth is likely to be

an important factor in the prevention of cardiovascular disease in India. In the meantime, it is important to find out if prevention of obesity in childhood could prevent disease in the low-birth-weight members of our population.

ACKNOWLEDGMENTS

The study was funded by the Wellcome Trust, London, and the Medical Research Council (U.K.).

We are grateful to the children, and their families, who took part, and to biochemists Dr. S.S. Naik and D.S. Bhat, medical social workers M. Hoge, D. Dhere, and A. Vairagar, and staff nurses Ms. Gaikwad and Ms. Gokhale, who made significant contributions to the study. We also thank Professor C.N. Hales, and his staff in the Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, U.K., for insulin assays and advice.

REFERENCES

1. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M: Rising prevalence of NIDDM in an urban population in India. *Diabetologia* 40:232–237, 1997
2. Reddy KS: Cardiovascular diseases in India. *World Health Stat Q* 46:101–107, 1993
3. Gupta R, Gupta VP: Meta-analysis of coronary heart disease prevalence in India. *Indian Heart J* 48:241–245, 1996
4. Bulatao RA, Stephens PW: *Global Estimates and Projections of Mortality by Cause, 1970–2015*. Washington, DC, Population and Human Resources Department, The World Bank, 1992 (Working Paper Ser., no. 1007)
5. Yajnik CS, Naik SS, Bhat DS, Joshi VM, Shelgikar KM, Alberti KGMM, Hockaday TDR: The relationship between obesity, plasma immunoreactive insulin concentration and blood pressure in newly diagnosed Indian type 2 diabetic patients. *Diabet Med* 10:146–151, 1993
6. Shelgikar KM, Naik SS, Khopkar M, Bhat DS, Raut KN, Joglekar CV, Gerard ME, Yajnik CS: Circulating lipids and cardiovascular risk in newly diagnosed non-insulin-dependent diabetic subjects in India. *Diabet Med* 14:757–761, 1997
7. Shelgikar KM, Hockaday TDR, Yajnik CS: Central rather than generalised obesity is related to hyperglycaemia in Asian Indian subjects. *Diabet Med* 8:712–717, 1991
8. McKeigue PM, Shah B, Marmot MG: Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 337:382–386, 1991
9. Neel JV: Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14:353–361, 1962
10. Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37:150–154, 1994
11. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell U, Leon DA: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 312:406–410, 1996
12. Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP: Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 37:624–631, 1994
13. Hales CN, Barker DJP: Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35:595–601, 1992
14. Mohan M, Prasad SR, Chellani HK, Kapani V: Intrauterine growth curves in north Indian babies: weight, length, head circumference and ponderal index. *Indian Pediatr* 27:43–51, 1990
15. Gopalan C: Low birth weight: significance and implications. In *Nutrition in Children: Developing Country Concerns*. Sachdev HPS, Chaudhury P, Eds. New Delhi, Imprint, 1994
16. Yajnik CS, Fall CHD, Vaidya U, Pandit AN, Bavdekar A, Bhat DS, Osmond C, Hales CN, Barker DJP: Fetal growth and glucose and insulin metabolism in four year old Indian children. *Diabet Med* 12:330–336, 1995
17. Kuppuswamy B: *Manual of Socio-Economic Status Scale*. Delhi, India, Manasayan Publications, 1962
18. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
19. Sobey WJ, Beer SF, Carrington CA, Clark PMS, Frank BH, Gray IP: Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65–66 split and 32–33 split proinsulin. *Biochem J* 260:535–541, 1989
20. Alpha B, Cox L, Crowther N, Clark PMS, Hales CN: Sensitive amplified immunoenzymometric assays (IEMA) for human insulin and intact proinsulin. *Eur J Clin Chem Clin Biochem* 30:27–32, 1992
21. Goran MI, Driscoll P, Johnson R, Nagy TR, Hunter G: Cross-calibration of body composition techniques against dual-energy X-ray absorptiometry in young children. *Am J Clin Nutr* 63:299–305, 1996
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
23. Phillips DIW, Clark PMS, Hales CN, Osmond C: Understanding oral glucose tolerance: comparison of glucose or insulin measurements during oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 11:286–292, 1994
24. Wareham NJ, Phillips DIW, Byrne CD, Hales CN: The 30-minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion (Letter). *Diabet Med* 12:931, 1995
25. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
26. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA: Cross-sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 73:17–24, 1995
27. Whincup PF, Cook DG, Adshead F, Taylor SJC, Walker M, Papacosta O, Alberti KGMM: Childhood size is more strongly related than size at birth to glucose and insulin levels in 10–11 year-old children. *Diabetologia* 40:319–326, 1997
28. Fall CHD, Stein CE, Kumaran K, Cox V, Osmond C, Barker DJP, Hales CN: Size at birth, maternal weight, and non-insulin dependent diabetes in South India. *Diabet Med* 15:220–227, 1998
29. Phillips DIW, Hirst S, Clark PMS, Hales CN, Osmond C: Fetal growth and insulin secretion in adult life. *Diabetologia* 37:592–596, 1994
30. Wills J, Watson JM, Hales CN, Phillips DIW: The relation of fetal growth to insulin secretion in young men. *Diabet Med* 13:773–774, 1996
31. Donker GA, Labarthe DR, Harris RB, Selwyn B, Wattigney W, Berenson GS: Low birthweight and serum lipid levels at age seven through eleven in a biracial sample. *Am J Epidemiol* 145:398–407, 1997
32. Fall CHD, Barker DJP, Osmond C, Winter PD, Clark PMS, Hales CN: Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *BMJ* 304:801–805, 1992
33. Fall CHD, Osmond C, Barker DJP, Clark PMS, Hales CN, Stirling Y, Meade TW: Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 310:428–432, 1995
34. Barker DJP, Martyn CN, Osmond C, Hales CN, Fall CHD: Growth in utero and serum cholesterol concentrations in adult life. *BMJ* 307:1524–1527, 1993
35. Mathai M, Thomas S, Peedicayil A, Regi A, Jaspaer P, Joseph R: Growth pattern of the Indian fetus. *Int J Gynecol Obstet* 48:21–24, 1995
36. Barker DJP: *Mothers, Babies and Health in Later Life*. Edinburgh, U.K., Churchill Livingstone, 1998
37. Kramer MS: Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Org* 65:663–737, 1987
38. Hattersley A, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S: Mutations in the glucokinase gene in the fetus result in reduced birthweight. *Nat Genet* 19:268–270, 1998
39. Crowther NJ, Cameron N, Trusler J, Gray IP: Association between poor glucose tolerance and rapid post-natal weight gain in seven-year-old children. *Diabetologia* 41:1163–1167, 1998
40. Law CM, Barker DJP, Osmond C, Fall CHD, Simmonds SJ: Early growth and abdominal fatness in adult life. *J Epidemiol Community Health* 46:184–186, 1992
41. Malina RM, Katzmarzyk PT, Beunen G: Birth weight and its relationship to size attained and relative fat distribution at 7 to 12 years of age. *Obesity Res* 4:385–390, 1996
42. Barker M, Robinson S, Osmond C, Barker DJP: Birthweight and body fat distribution in adolescent girls. *Arch Dis Child* 77:381–383, 1997
43. Goran MI, Kaskoun M, Shuman WP: Intra-abdominal adipose tissue in young children. *Int J Obesity* 19:279–283, 1995
44. Randle PJ, Garland PB, Hales CN, Newsholme EA: The glucose fatty acid cycle. *Lancet* i:785–789, 1963
45. Zimmet P, Hodge A, Nicolson M, Staten M, de Courteen M, Moore J, Morawiecki A, Lubina J, Collier G, Alberti G, Dowse G: Serum leptin concentration, obesity and insulin resistance in western Samoans: a cross-sectional study. *BMJ* 313:965–969, 1997
46. Hotamisligil GS, Spielelman BM: Tumor necrosis factor α: a key component of obesity-diabetes link. *Diabetes* 43:1271–1278, 1994
47. Tanner JM: Growth as a target-seeking function: catch-up and catch-down growth in man. In *Human Growth, A Comprehensive Treatise, Volume 1:*

Developmental Biology and Prenatal Growth. Falkner F, Tanner JM, Eds. New York, London, Plenum, 1986
48. Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, Lithell U-B, McKeigue PM: Failure to realise growth potential in utero, and adult obesity, in relation to blood pressure in 50-year old Swedish men. *BMJ* 312:410–416, 1996
49. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D: Childhood growth and age at menarche. *Br J Obstet Gynecol* 103:814–817, 1996
50. Clark PM, Hindmarsh PC, Shiell AW, Law CM, Honour JW, Barker DJP: Size at birth and adrenocortical function in childhood. *Clin Endocrinol* 45:721–726, 1996
51. Tanner JM: The interaction of heredity and environment in the control of growth. In *Foetus Into Man.* Ware, U.K., Castlemead, 1989
52. Hattersley AT, Tooke JE: The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 353:1789–1792, 1999
53. Law CM, de Swiet M, Osmond C, Fayers PM, Barker DJP, Cruddas AM, Fall CHD: Initiation of hypertension in utero and its amplification throughout life. *BMJ* 306:24–27, 1993
54. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJP: Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 318:427–431, 1999
55. Sachdev HPS: Nutritional status of children and women in India: recent trends. *Bull Nutr Found India* 18:1–5, 1997