Birth Weight, Type 2 Diabetes, and Insulin Resistance in Pima Indian Children and Young Adults

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OBJECTIVE — To investigate the mechanisms underlying the association between birth weight and type 2 diabetes in a population-based study of 3,061 Pima Indians aged 5–29 years.

RESEARCH DESIGN AND METHODS — Glucose and insulin concentrations were measured during a 75-g oral glucose tolerance test, and insulin resistance was estimated according to the homeostatic model (homeostasis model assessment–insulin resistance [HOMA-IR]). Relationships between birth weight, height, weight, fasting and postload concentrations of glucose and insulin, and HOMA-IR were examined with multiple regression analyses.

RESULTS — Birth weight was positively related to current weight and height ($P < 0.0001$, controlled for age and sex, in each age-group). The 2-h glucose concentrations showed a U-shaped relationship with birth weight in subjects >10 years of age, and this relation was independent of current body size. In 2,272 nondiabetic subjects, after adjustment for weight and height, fasting and 2-h insulin concentrations and HOMA-IR were negatively correlated with birth weight.

CONCLUSIONS — Low-birth-weight Pimas are thinner at ages 5–29 years, yet they are more insulin resistant relative to their body size than those of normal birth weight. By contrast, those with high birth weight are more obese but less insulin resistant relative to their body size. The insulin resistance of low-birth-weight Pima Indians may explain their increased risk for type 2 diabetes.

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Associations between low birth weight and increased risk of type 2 diabetes in adult life have been described in various populations (1–5). The association has been explained etiologically as representing long-term effects of nutritional deprivation in utero on fetal growth and on the development of the endocrine pancreas (6,7), as a selective survival of small babies genetically predisposed to diabetes and insulin resistance (5), or as the effect of genes causing both low birth weight and later abnormalities of insulin secretion or sensitivity (8,9). Whether the relationship between diabetes and low birth weight is mediated through reduced insulin secretion (2,6,10) or insulin resistance (3,11–13) remains uncertain.

Pima Indians residing in the Gila River Indian Community in central Arizona have the world's highest recorded prevalence and incidence of type 2 diabetes (14,15). We have previously shown that the prevalence of diabetes in children and young adults is higher in subjects with either low or high birth weight (5,16). The purpose of the present study is to investigate the mechanisms underlying the association between birth weight and type 2 diabetes in a population-based study of Pima Indian children, adolescents, and young adults.

RESEARCH DESIGN AND METHODS

— Since 1965, a longitudinal study of diabetes and its complications has been conducted among the American Indian population of the Gila River Indian Community in Arizona. All residents aged ≥5 years have been invited to participate in research examinations every ~2 years, regardless of health status (14). Standardized biennial examinations include measurements of venous plasma glucose 2 h after a 75-g oral glucose load and, since 1973, of plasma glucose and serum insulin, at fasting and 2 h after the glucose load.

Here we report on people whose heritage is at least half Pima or Tohono O'odham or a mixture of these two closely related tribes and who have had at least one 75-g oral glucose tolerance test between 1965 and 1997 when they were 5–29 years of age. Diabetes was diagnosed by World Health Organization criteria (17). Weight and height were measured. Because BMI is highly height dependent and, therefore, a poor indicator of obesity in children, we used relative weight (the ratio of each person's weight to a predicted weight, expressed as a percentage) to assess obesity. Predicted weight was calculated with linear regression analysis in each age-group and sex, as a function of age and height. Birth weights were obtained from medical records.

The relationship between birth weight and the prevalence of diabetes or glucose concentrations was assessed in 3,061 subjects examined at ages 5–29 years between 1965 and 1997. Of these subjects, 2,272 who were nondiabetic and had one or more measurements of serum insulin concentration between 1973 and 1997 were used in all other analyses.

Plasma glucose concentration was measured by an autoanalyzer using the

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Abbreviations: HOMA-IR, homeostasis model assessment–insulin resistance; RIA, radioimmunoassay.

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

Table 1—*Anthropometric and biochemical variables by age-group and birth-weight group*

Age-group (years)	*n* (M/F)	Birth weight (kg)	Fasting insulin (pmol/l)	Postload insulin (pmol/l)	Fasting glucose (mmol/l)	Postload glucose (mmol/l)	Weight (kg)	Height (cm)
5–9	906/968	<2.5	161 (31)	635 (31)	4.84 (39)	5.35 (62)	32.7 (71)	130.1 (71)
		2.5–3.5	136 (347)	626 (347)	5.31 (468)	5.31 (828)	32.6 (960)	129.2 (961)
		3.5–4.5	142 (302)	622 (302)	4.84 (412)	5.26 (686)	34.7 (786)	130.8 (787)
		≥4.5	127 (19)	691 (19)	4.87 (28)	5.49 (46)	40.6 (54)	133.9 (54)
10–14	1,114/1,209	<2.5	242 (50)	1,379 (50)	5.14 (60)	6.39 (84)	60.7 (87)	156.0 (86)
		2.5–3.5	235 (671)	1,066 (671)	5.10 (785)	5.83 (1,179)	61.6 (1,205)	157.6 (1,204)
		3.5–4.5	229 (548)	999 (548)	5.22 (638)	6.54 (926)	64.7 (955)	159.2 (954)
		≥4.5	247 (41)	1,019 (41)	5.69 (52)	7.01 (67)	73.6 (72)	161.1 (72)
15–19	764/974	<2.5	227 (52)	1,048 (52)	5.42 (59)	7.01 (69)	74.2 (69)	162.4 (69)
		2.5–3.5	221 (669)	965 (669)	5.24 (725)	6.05 (926)	76.5 (936)	164.1 (935)
		3.5–4.5	217 (493)	884 (493)	5.24 (541)	5.96 (671)	82.6 (681)	167.2 (681)
		≥4.5	240 (35)	837 (35)	6.05 (41)	7.53 (46)	88.6 (49)	168.5 (49)
20–29	555/834	<2.5	266 (46)	1,042 (46)	6.38 (56)	8.72 (57)	86.9 (57)	162.6 (58)
		2.5–3.5	271 (581)	1,123 (581)	6.02 (682)	7.67 (747)	90.4 (764)	164.2 (764)
		3.5–4.5	261 (409)	970 (409)	6.15 (497)	7.68 (508)	96.8 (521)	167.2 (521)
		≥4.5	290 (27)	999 (27)	6.42 (38)	8.59 (40)	42 (106.4)	169.3 (42)

Data are geometric means (*n*). For analyses of glucose, weight, and height, data from the last examination in each age-group were used for each subject. For analyses of insulin, data were used from the last examination in each age-group at which the subject was nondiabetic.

potassium ferricyanide method between 1965 and 1991 and the hexokinase method from 1991 onward. The two methods were highly correlated and gave nearly identical results. Serum insulin concentration was determined with the Herbert modification (18) of the radioimmunoassay (RIA) of Yalow and Berson (19) between 1973 and 1986, and it has been determined with Autopak Insulin RIA (Concept 4; ICN Biomedicals, Horsham, PA) since 1987. There were systematic differences between the two assays. To allow the use of all available measurements of insulin concentration, a corrected insulin variable was computed using regression equations with a quadratic term from the new to the old method. All analyses were also performed separately on two smaller samples, each composed of insulin concentrations by the same method, and the results were similar to those reported here.

Computations were performed in the age-groups 5–9, 10–14, 15–19, and 20–29 years. For analyses of diabetes, abnormal glucose tolerance, obesity, and plasma glucose concentration, data from the last examination in each age-group were used for each subject. For analyses of serum insulin concentration, data were used from the last examination in each age-group at which the subject was nondiabetic. Subjects were included more than once if they were examined in more than one age-group.

In statistical analyses, the distributions of glucose and insulin concentrations were normalized by log-transformation. The significance of differences in the prevalence of diabetes according to birth weight was analyzed by a Mantel-Haenszel χ^2 test controlled for age and sex.

Relationships between birth weight, height, weight, and fasting and postload concentrations of glucose and insulin were examined with multiple regression analyses. Estimates of insulin resistance (fasting glucose [mg/dl]) × (fasting insulin [μU/ml] ÷ 22.5), homeostasis model assessment–insulin resistance (HOMA-IR) derived from the homeostatic model (20), were also analyzed. Of several commonly used estimates of insulin resistance based on fasting and 2-h serum insulin concentrations in nondiabetic people, the HOMA-IR had the highest correlation (−0.62) with insulin sensitivity derived from the hyperinsulinemic-euglycemic clamp in adults (R.L.H., unpublished observations). Because logarithms of the outcome variables (fasting insulin, 2-h insulin, and HOMA-IR) were used, the regression coefficients were exponentiated to obtain estimates of proportional differences associated with a specified difference in the predictor variable. Interaction terms between birth weight and height and between birth weight and weight were initially included in the multiple regression analyses but were not significantly associated with the response variables and were thus omitted from the final analyses. The linearity of associations of birth weight with the outcome variables was tested by means of a quadratic term to account for nonlinear associations. This quadratic term was included in the final model only when it contributed significantly to the model.

RESULTS — Table 1 shows the geometric means of weight, height, serum insulin, and plasma glucose concentrations, measured in subjects at the last examination in each age-group and stratified by birth weight in four categories. Fasting and postload glucose and insulin concentrations tended to be higher in subjects with low (<2.5 kg) and high (≥4.5 kg) birth weight than in those whose birth weight had been normal. Birth weight was positively and linearly related to current weight and height (weight: $r = 0.15$ at 5–9 years, $r = 0.14$ at 10–14 years, $r = 0.17$ at 15–19 years, and $r = 0.18$ at 20–29 years; height: $r = 0.15$ at age 5–9, $r = 0.22$ at age 10–14, $r = 0.24$ at age 15–19, and $r = 0.14$ at age 20–29 years, $P < 0.0001$, controlled for age and sex, in each age-group). Weight and height are, therefore, potential confounders of the relations between birth weight and glucose and insulin concentrations. The relationship between birth weight and relative weight was quadratic, significantly so

for age-groups 5–9 (P = 0.03) and 10–14 years (P = 0.005, Fig. 1). Subjects with low birth weight were, on average, shorter and thinner, while those with high birth weight were taller and more obese.

The prevalence of type 2 diabetes according to birth weight and age-group is shown in Fig. 2. The prevalence of diabetes shows a U-shaped relationship with birth weight, with higher rates in those in the highest and in the lowest birth-weight groups ($P < 0.001$, controlled for age and sex).

Mean 2-h plasma glucose concentrations by birth weight are shown in Fig. 3. Postload glucose concentrations show a U-shaped relationship with birth weight in age-groups 10–14, 15–19, and 20–29 years, and this association is independent of current weight and height ($P < 0.01$ for each age-group, adjusted for age, sex, and birth date or for age, sex, birth date, height, and weight).

Mean serum insulin concentrations, by birth weight and tertiles of relative weight, are presented in Figs. 4 (fasting insulin) and 5 (postload insulin). For each age-group, the highest mean insulin levels were observed in subjects who were lightest at birth but who had the greatest weight for height in childhood, adolescence, or adulthood. The inverse relationship between birth weight and insulin was stronger in the heaviest subjects (highest tertile of relative weight), but significantly so only for the 2-h insulin concentrations in the 20- to 29-year-old age-group (P = 0.01).

There was a linear and negative relationship between birth weight and insulin (both fasting and 2-h) when adjusted for current weight and height, with the highest insulin concentrations in those in the lowest birth-weight group. The relationship of fasting and postload serum insulin concentrations and HOMA-IR with the predictor variables are shown in Table 2. Birth weight was inversely and significantly related to insulin concentrations and HOMA-IR in all age-groups, except the 10- to 14-year-old age-group. However, in each age-group, the differences in insulin concentrations and in the HOMA-IR were greater for a 1 SD difference in weight (adjusted for height) than for a 1 SD difference in birth weight. Other important determinants of insulin concentrations and HOMA-IR were birth date and female sex (for all age-groups except the 20- to 29-year-old age-group). The positive coefficient of birth date in each model indicates that subjects born more recently were more hyperinsulinemic or insulin resistant when the values of the other variables in Table 2 were included.

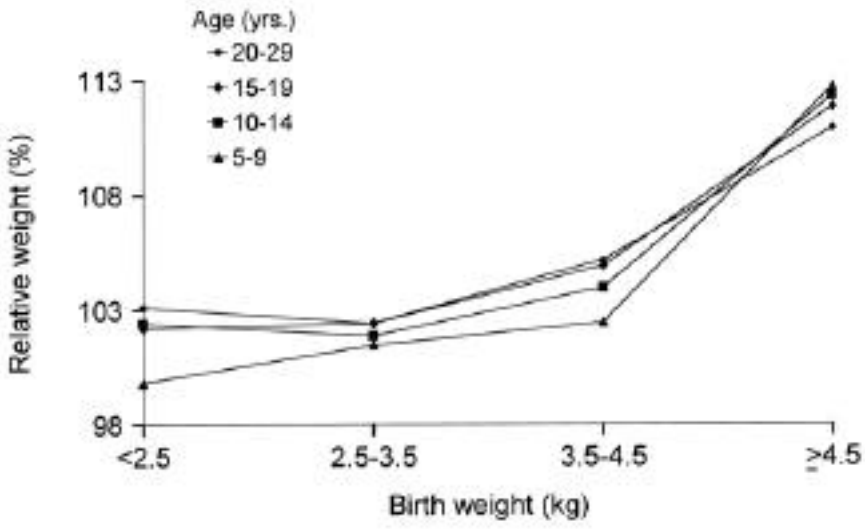

Figure 1—*Mean relative weight by birth weight in age-groups 5–9, 10–14, 15–19, and 20–29 years. Data are adjusted for age, sex, and birth date.*

CONCLUSIONS — In Pima Indian children and young adults, birth weight is inversely associated with fasting and 2-h insulin levels, and with insulin resistance estimated from the homeostatic model, when adjusted for current weight and height. We were not able to assess the relationship between birth weight and insulin secretion, since we do not have adequate estimates of β-cell function. Both fasting and 2-h insulin concentrations are correlated with insulin resistance in normoglycemic adults (21) and in nondiabetic Pima Indian adults (R.L.H., unpublished observations). It seems, therefore, that low-birth-weight Pima Indians are more insulin resistant than expected for their current height and weight. These findings are consistent with the hypotheses that nutritional deprivation in utero causes more insulin resistance later in life (11), that low-birth-weight babies predisposed to insulin resistance and type 2 diabetes have a survival advantage (5), or that certain genes influence

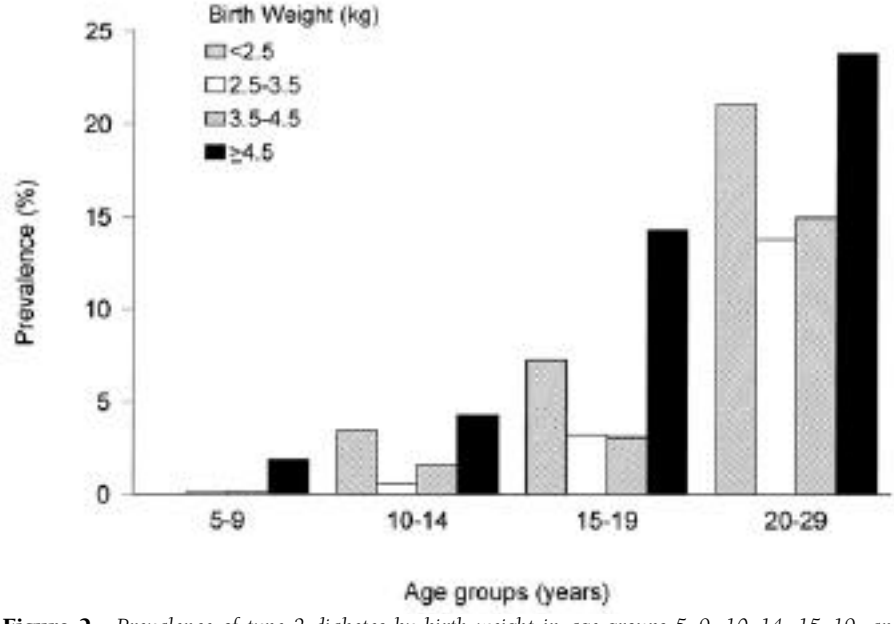

Figure 2—*Prevalence of type 2 diabetes by birth weight in age-groups 5–9, 10–14, 15–19, and 20–29 years.* P = *0.001 (Mantel-Haenszel* χ^2 *test, controlled for age and sex).*

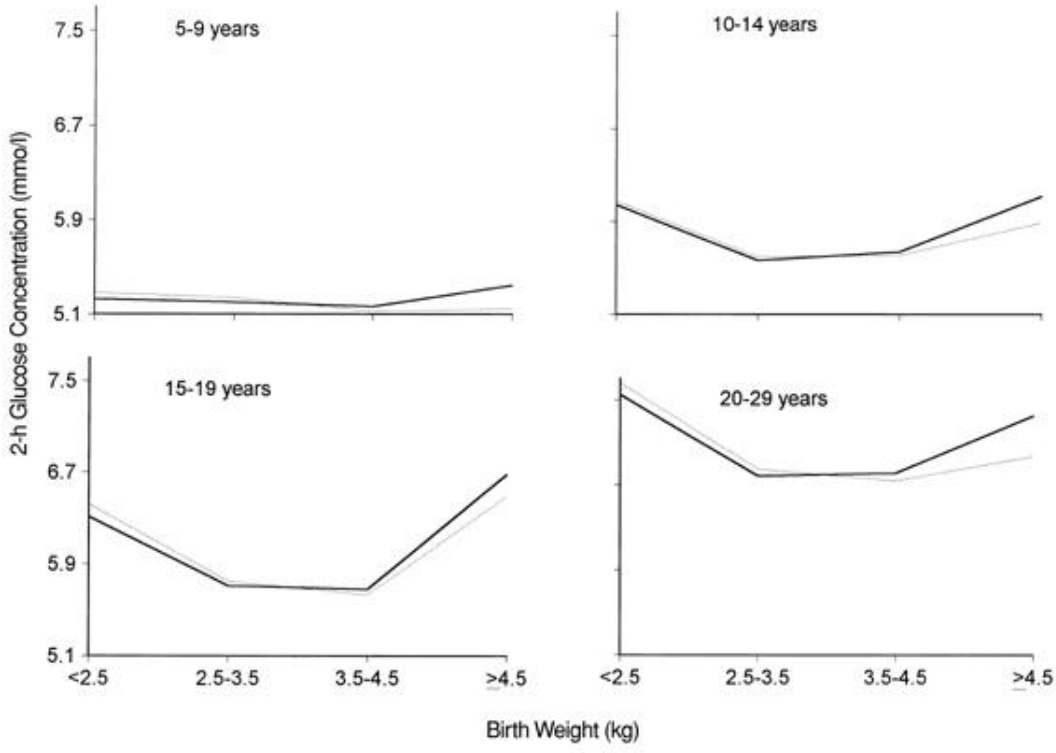

Figure 3—*Geometric mean values of 2-h glucose concentration by birth weight in age-groups 5–9, 10–14, 15–19, and 20–29 years. Data are adjusted for age, sex, and birth date; dotted lines indicate effect of additional adjustment for weight and height.*

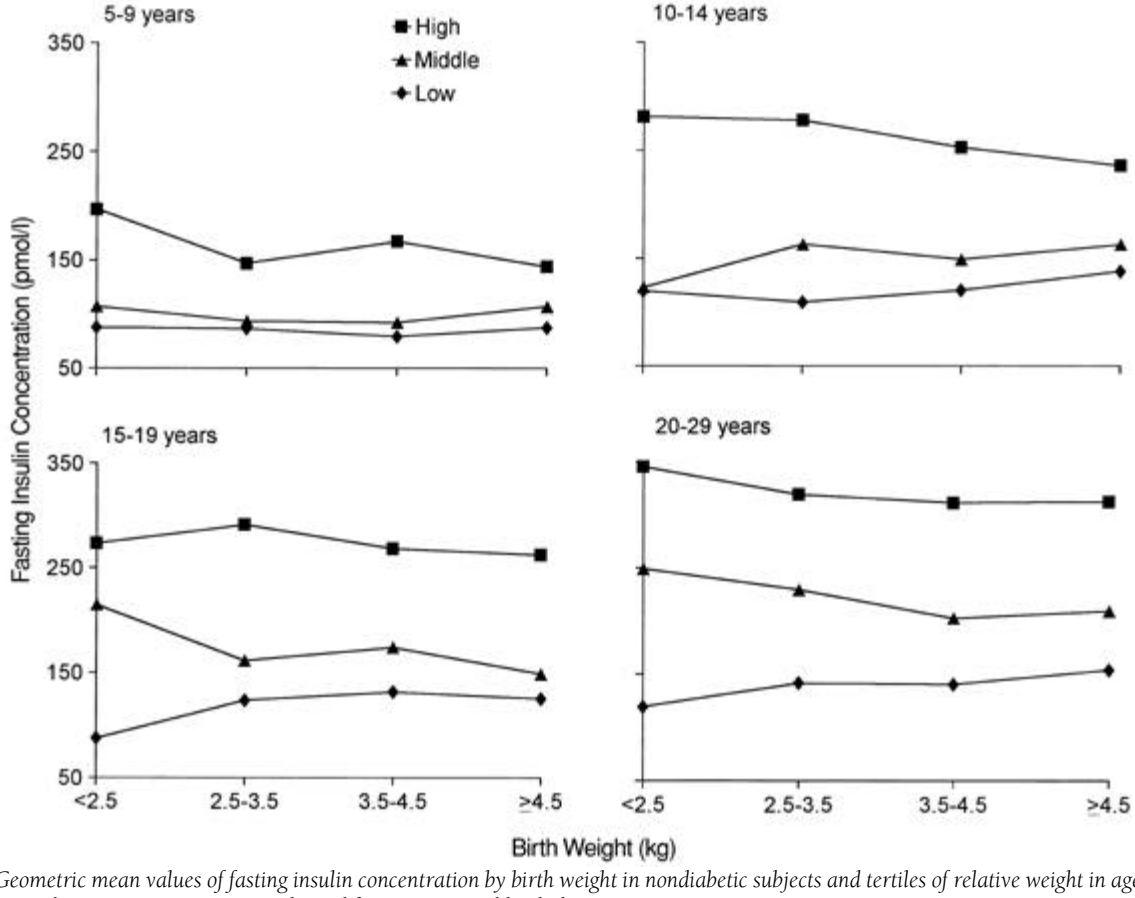

Figure 4—*Geometric mean values of fasting insulin concentration by birth weight in nondiabetic subjects and tertiles of relative weight in age-groups 5–9, 10–14, 15–19, and 20–29 years. Data are adjusted for age, sex, and birth date.*

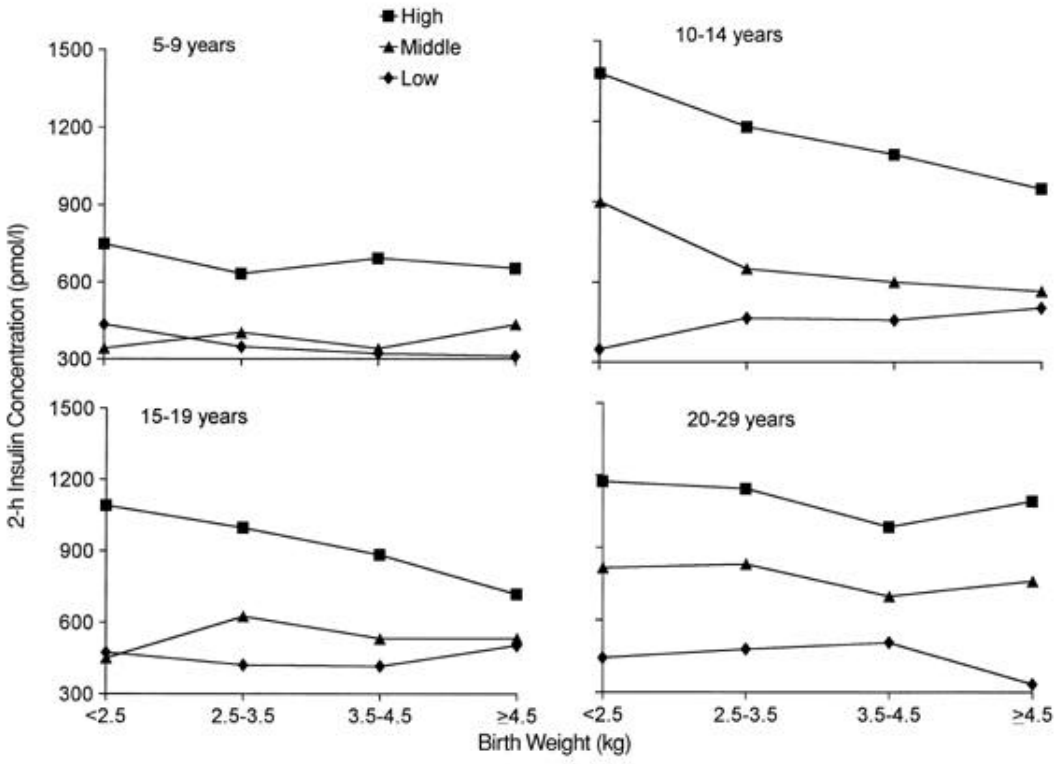

Figure 5—*Geometric mean values of 2-h insulin concentration by birth weight in nondiabetic subjects and tertiles of relative weight in age-groups 5–9, 10–14, 15–19, and 20–29 years. Data are adjusted for age, sex, and birth date.*

both birth weight and later abnormalities of insulin secretion or action (8,9).

Similar results have been discussed in 10- to 11-year-old British children (22), in 4-year-old Indian children (23), and in adults (3,4). In a recent study of young healthy Danes, the insulin sensitivity index (estimated from the frequently sampled intravenous glucose tolerance test) was significantly inversely correlated with birth weight, but no association between birth weight and β-cell function (estimated from the response to intravenous glucose) was noted (24).

Although low birth weight influences insulin resistance in Pima Indian children and young adults, other factors, particularly the degree of obesity, play a relatively much more important role in determining its extent (Table 2), as has also been suggested in Caucasian children (22) and young adults (24,25). There are also temporal trends in insulin sensitivity in the Pimas. Later-born individuals are more insulin resistant, regardless of their age, sex, birth weight, and degree of obesity (Table 2). This observation is also consistent with the increasing prevalence of diabetes in Pima Indian children (16), and it may reflect the other important lifestyle changes that influence insulin resistance that have occurred in this population during the past 30 years.

The relationship between birth weight or size at birth and glucose concentrations reported in other children has been inconsistent, possibly because of differing childhood susceptibility to glucose intolerance. In a British study of 7-year-old subjects, ponderal index at birth (but not birth weight) was inversely related to 30-min postload glucose concentration (27). In 4-year-old Indian children, birth weight was negatively correlated with 30-min postload glucose levels (23). However, in a recent study of 10- to 11-year-old British children, neither birth weight nor ponderal index at birth was consistently related to glucose concentrations, with or without adjustment for childhood height and ponderal index (22). In Pima Indians, the U-shaped relationship between birth weight and 2-h glucose concentration was evident in subjects as young as 10 years of age and consistent in the older age-groups, and it was independent of current weight and height.

Low birth weight is associated with a high prevalence of type 2 diabetes in British adults (1,2,26). Although low birth weight is associated with diabetes in Pima children and young adults, there is also a high prevalence of diabetes in those with high birth weights (5). This results in a U-shaped relationship between birth weight and diabetes in Pima Indians, which is also found in children as young as 10 years of age (16). The U-shaped relationship between birth weight and impaired glucose tolerance found in children (not shown) was not consistent in the older age-groups. However, the U-shaped association between birth weight and glucose concentrations consistently found in Pima children and young adults supports the conclusion that both low- and high-birth-weight Pimas are at risk for developing type 2 diabetes. The increased risk of diabetes among Pimas with high birth weight was largely explained by maternal diabetes during pregnancy (5). In offspring of mothers who did not have diabetes during pregnancy, birth weight relationship with the prevalence of diabetes and abnormal glucose tolerance was still U-shaped in the age-groups 10–14 and 15–19 years, but it became linear and negative in the age-groups 5–9 and 20–29 years. Exposure to diabetes in utero largely accounts for the increasing prevalence of type 2 diabetes in Pima Indian children (16). Adding exposure to intrauterine diabetes to the multi-

Table 2—*Proportional differences in serum insulin concentrations and HOMA-IR*

Predictor variables	Fasting insulin			2-h insulin			HOMA-IR		
	Difference (%)	95% CI	*P* value	Difference (%)	95% CI	*P* value	Difference (%)	95% CI	*P* value
Age 5–9 years									
Age	−0.8	−7 to 10	0.7	−4	−12 to 10	0.3	−0.2	−8 to 56	0.9
Sex	21	12 to 30	0.0001	34	22 to 48	0.0001	19	10 to 43	0.0001
Birth date	35	28 to 42	0.0001	9	1 to 17	0.02	35	27 to 43	0.0001
Height	8	−10 to 18	0.1	−0.4	−14 to 9	0.9	9	−10 to 19	0.09
Weight	41	34 to 48	0.0001	46	41 to 63	0.0001	43	36 to 51	0.0001
Birth weight	−5	−9 to −2	0.004	−8	−13 to −2	0.003	−5	−9 to −1	0.01
Age 10–14 years									
Age	−5	−8 to −1	0.004	−0.6	−5 to 10	0.8	−5	−9 to −2	0.002
Sex	21	14 to 28	0.0001	15	37 to 61	0.0001	18	11 to 25	0.0001
Birth date	28	23 to 33	0.0001	20	13 to 28	0.0001	28	22 to 33	0.0001
Height	−6	−16 to 10	0.2	−29	−47 to −13	0.0002	−6	−16 to 10	0.2
Weight	47	45 to 55	0.0001	58	51 to 67	0.0001	53	48 to 59	0.0001
Birth weight	−2	−4 to 10	0.2	−7	−11 to −3	0.0003	−2	−5 to 1	0.07
Age 15–19 years									
Age	−3	−8 to 10	0.8	−2	−5 to 10	0.3	−0.7	−3 to 10	0.5
Sex	13	5 to 23	0.002	50	33 to 69	0.0001	9	5 to 19	0.04
Birth date	46	40 to 52	0.0001	28	20 to 37	0.0001	47	40 to 54	0.0001
Height	−12	−17 to −8	0.0001	−22	−30 to −15	0.0005	−14	−19 to −9	0.0001
Weight	47	42 to 51	0.0001	46	39 to 52	0.0001	53	48 to 57	0.0001
Birth weight	−4	−7 to −1	0.003	−8	−12 to −3	0.0005	−4	−8 to −1	0.004
Age 20–29 years									
Age	1	0.2 to 2	0.01	0.3	−10 to 2	0.7	1	0 to 1.1	0.04
Sex	9	−10 to 31	0.07	38	21 to 57	0.0001	5	−10 to 15	0.3
Birth date	30	−10 to 19	0.0001	5	−10 to 13	0.2	22	16 to 30	0.0001
Height	−10	−15 to −5	0.0001	−19	−27 to −11	0.0001	−11	−17 to −6	0.0001
Weight	58	52 to 64	0.0001	59	50 to 68	0.0001	66	60 to 73	0.0001
Birth weight	−5	−8 to −2	0.03	−6	−11 to −1	0.01	−6	−9 to −2	0.001

Difference (%) is a multiple linear regression coefficient transformed to represent the percentage difference in the insulin variable associated with a specified difference in each of the predictor variables. These differences were 1 year (age), female versus male (sex), 10 years (birth date), and 1 SD (height, weight, and birth weight). Data used were from the last exam in each age-group at which the subject was nondiabetic.

ple regression analyses with insulin and HOMA-IR as response variables, however, did not substantially influence the results.

In Pima Indian children and young adults, lower birth weight is associated with higher serum insulin concentration (and presumably lower insulin sensitivity), especially when related to their smaller body size. In conclusion, low-birth-weight Pima Indians are more insulin resistant than those with normal birth weight, and this may explain their increased risk for type 2 diabetes.

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