

Effects of Low Birth Weight on Insulin Resistance Syndrome in Caucasian and African-American Children

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OBJECTIVE — To examine the effects of low birth weight (LBW) on the components of insulin resistance syndrome (IRS) in Caucasian and African-American children aged 4–14 years ($n = 560$ observations among 139 subjects).

RESEARCH DESIGN AND METHODS — A linear random-effects modeling analysis with repeated measures (average four annual visits per child) was conducted to examine the associations between LBW and the components of IRS and their developmental trends over age. Fasting glucose, insulin, and lipids were assessed after an overnight fast; insulin action and secretion were determined by the tolbutamide-modified frequently sampled intravenous glucose tolerance test; and body composition was assessed by dual energy X-ray absorptiometry and computed tomography.

RESULTS — LBW was significantly associated with increased fasting insulin concentration and visceral fat mass, decreased acute insulin response, β -cell function, and HDL cholesterol among African-American children. Among children with LBW, there were significant differences in fasting insulin, insulin sensitivity, acute insulin response, and HDL cholesterol between Caucasians and African-Americans. LBW was significantly associated with faster decrease in acute insulin response and increase in triglycerides with regard to age. The hyperbolic function between insulin sensitivity and β -cell function was retarded among children with LBW ($P = 0.04$). In addition, there was a significant interaction between LBW and ethnicity in relation to fasting insulin ($P < 0.05$) and visceral fat ($P = 0.05$).

CONCLUSIONS — LBW may predict the risk of the IRS and its progression over age in childhood, and this effect may be more pronounced among African-American children.

Diabetes Care 24:2035–2042, 2001

Insulin resistance syndrome (IRS), also referred to as syndrome X or metabolic syndrome, has been postulated to comprise hyperinsulinemia, glucose intolerance, low HDL cholesterol, elevated triglycerides, obesity, and hypertension (1). Presence of one or more components of IRS may increase risk for coronary heart disease and type 2 diabetes (1). Studies in Europe, North America, and

Asia have consistently shown that low birth weight (LBW) increases risk of the IRS, coronary heart disease, and type 2 diabetes in middle-aged and elderly adults (2–8) as well as young adults (9–11).

However, whether the association between LBW and the components of IRS holds in children is far from clear. Several recent studies have reported the inconsis-

tent effects of LBW on IRS in children of different ages and ethnicities. For example, LBW was associated with increased glucose and insulin concentration in 4-year-old Indian children (12) and most of the IRS components in healthy 8-year-old Indian children (13). In contrast, studies in Britain reported that thinness at birth (but not birth weight) was related to higher plasma glucose concentration in 7-year-old Caucasian children (14); however, there was no relation between LBW and glucose intolerance in children aged 10–11 years (15). Interestingly, a U-shaped relation between birth weight and postload glucose concentrations was detected among Pima Indian children aged 10–14 years in the U.S. (16). LBW and rapid childhood gains in weight were found to predict glucose tolerance in 7-year-old black South African children (17). However, to our knowledge, no such studies have been conducted in African-American children.

All of the previous studies among children were cross-sectional. In contrast, a longitudinal design, in which a response variable is measured repeatedly on each individual over time, enables assessment of changes in an individual's response as time changes (18). In addition, none of the previous studies in children have used advanced technology to measure insulin action and secretion, as well as body composition and fat distribution, especially among African-American children. Such studies may be important, based on previous studies showing that fasting insulin is higher and insulin sensitivity is lower among African-American children regardless of body fat or fat distribution (19,20).

Therefore, the objective of this study was to examine the differential effect of LBW on the components of IRS between Caucasian and African-American children and to determine the effect of LBW on developmental trends in components of IRS during growth from 4–14 years of age. We hypothesized that the effect of LBW on the aspects of IRS may differ between Caucasian and African-American

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Received for publication 3 April 2001 and accepted in revised form 17 August 2001.

Abbreviations: AIR, acute insulin response; IRS, insulin resistance syndrome; LBW, low birth weight; NBW, normal birth weight; S_i , insulin sensitivity.

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

children and that LBW may exert adverse effects on the developmental trends of certain components of IRS with regard to age and total fat mass.

RESEARCH DESIGN AND METHODS

Study design and subjects

Study subjects were part of an ongoing longitudinal study of intra-abdominal fat and disease risk in children (19). The current study used data from 139 children (86 Caucasians, 53 African-Americans) aged 4–12 years (mean 8.1) at the start of the study and 8–14 years (mean 11.7) at the end of the study. Ethnicity was determined by self-report, based on both parents and both sets of grandparents being of the same ethnicity. This study used an accelerated longitudinal design by which limited longitudinal data on a specific age cohort can be linked to determine a common developmental trend over time (21). Children were followed annually for 3–5 years with an average of four repeated measures for each subject, which resulted in a total of 560 observations. The children were recruited from Birmingham, AL, and had been free of major illnesses since birth. The nature, purpose, and possible risks of the study were carefully explained to the parents before consent was obtained. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. All measurements were performed at the General Clinical Research Center and the Department of Nutritional Sciences at the University of Alabama at Birmingham during the school year (Fall and Spring) between 1994 and 1999.

Protocol

At each annual visit, children were admitted to the General Clinical Research Center in the late afternoon for an overnight visit. Anthropometric measurements, including sexual maturation, were obtained. After 2000, only water and energy-free, noncaffeinated beverages were permitted until after the morning testing. In the morning after an overnight fast, blood was collected for hormone analysis and a tolbutamide-modified frequently sampled intravenous glucose tolerance test was performed. Two weeks later, the children arrived at the Energy Metabolism Research Unit at 0700 in the fasted state. Body composition was deter-

mined by dual-energy X-ray absorptiometry.

Assessment of birth weight, body weight, and height

The original data on birth weight were obtained by parental recall. The subjects whose birth weight was <2,500 g (or 5.5 lb) were categorized as LBW, and those whose birth weight was \geq 2,500 g were categorized as normal birth weight (NBW). Body weight during study visits was measured to the nearest 0.1 kg while subjects were wearing only light clothing. Height was measured to the nearest 0.5 cm with the subject standing without shoes, with heels together, and with the head in the horizontal plane.

Assessment of sexual maturation

Tanner's criteria were used to estimate sexual maturation on the scale of 1–5, with stage 1 representing prepubertal and 5 representing adult (22,23). The same pediatrician assessed Tanner stage in all the children. Tanner stage was regrouped as 1 (stage 1), 2 (stage 2), and 3 (stage 3 or above) in current study.

Measures of body composition and fat distribution

Subcutaneous abdominal adipose tissue and intra-abdominal adipose tissue (or visceral fat) were measured by computed tomography with a HiLight/Advantage Scanner (General Electric, Milwaukee, WI) as described previously (24). Body composition (fat mass and fat-free mass) was measured by dual-energy X-ray absorptiometry using a Lunar DPX-L densitometer (Lunar Radiation, Madison, WI), as described previously (25).

Tolbutamide-modified frequently sampled intravenous glucose tolerance test

Insulin sensitivity and the acute response to intravenous glucose were determined using the frequently sampled tolbutamide-modified intravenous glucose tolerance test, as described previously (19). In brief, at time 0, glucose (25% dextrose, 11.4% g/m²) was administered intravenously. Blood samples (2.0 ml) were then collected at the following times relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. Tolbutamide (125 mg/m²) was injected intravenously at 20 min. Sera were analyzed for glucose

and insulin, as described previously (19), and values were entered into the MINMOD computer program (Version 3.0; Richard N. Bergman, Los Angeles, CA) for determination of insulin sensitivity (S_i). Acute insulin response (AIR), based on the area above baseline insulin concentration, was calculated by the trapezoidal method during 0–10 min. The disposition index was calculated from the product of S_i and the AIR ($S_i \times \text{AIR}$) and used as an index of β -cell function (26).

Determination of blood lipids

HDL cholesterol and triglyceride were measured with the Ektachem DT II System (Johnson & Johnson Clinical Diagnostics, Rochester, NY). With this system, HDL cholesterol is measured after precipitation of LDL and VLDL with dextran sulfate and magnesium chloride. Control sera of low- and high-substrate concentration are analyzed with each group of samples, and values for these controls must fall within accepted ranges before samples were analyzed. The Ektachem DT II system is calibrated every 6 months with reagents supplied by the manufacturer.

Statistical analysis

A linear random-effects (or termed mixed-effects) modeling approach was conducted to capture the within- and between-subject variations in this longitudinal study. The major advantages of the linear random-effects model are its ability to account for the correlations appropriately between measurements inherent in a longitudinal study and its flexibility of modeling variations in variance and covariance of random-effect variables (27).

Fasting insulin, insulin sensitivity, AIR, disposition index, HDL cholesterol, and triglyceride were not normally distributed and, therefore, were log-transformed before data analyses. To obtain appropriate interpretations of intercepts (mean levels) and slopes (average trends) and to avoid possible collinearity in the random-effects models, age and other time-variant covariates (such as total fat mass) were further centered to their grand mean levels (i.e., original scores subtract from the grand means). The SAS PROC MIXED procedure (SAS Institute, Cary, NC) (28) was used to test the hypothesis proposed previously.

Table 1—Demographic characteristics at baseline and average values over repeated measures for physical and metabolic variables by birthweight group

Variable	Low birth weight (<2.5 kg, $n = 29$, 104 observations)	Normal birth weight (≥ 2.5 kg, $n = 110$, 456 observations)	<i>P</i>
Gender (% boys)*	41.4	38.2	0.75
Ethnicity (% white)*	51.7	64.6	0.21
Tanner stage (%)*			0.63
Stage 1	91.8	96.5	
Stage 2+	8.2	3.5	
Age (years)*	7.9 (7.3–8.5)	8.1 (7.8–8.4)	0.54
Weight (kg)	40.4 (37.5–43.3)	41.6 (39.5–43.7)	0.37
Height (cm)	137.3 (134.9–139.6)	140.3 (139.0–141.6)	0.02
Systolic blood pressure (mmHg)	110.3 (107.3–113.3)	109.2 (107.9–110.6)	0.55
Total fat mass (kg)	9.9 (8.0–12.4)	10.0 (8.9–11.3)	0.98
Total lean mass (kg)	24.5 (23.3–25.9)	25.7 (25.0–26.6)	0.16
Intra-abdominal adipose tissue (cm ²)	33.0 (27.1–40.5)	29.3 (26.3–32.8)	0.30
Subcutaneous abdominal adipose tissue (cm ²)	91.8 (67.4–125.2)	87.4 (71.5–96.5)	0.57
Fasting insulin (μ U/dl)	14.4 (12.4–16.8)	11.7 (10.8–12.7)	0.03
Fasting glucose (mg/dl)	92.5 (90.4–94.6)	92.6 (91.6–93.7)	0.91
S_i ($\times 10^{-3} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{dl}^{-1}$)	3.99 (2.92–5.42)	4.00 (3.53–4.57)	0.99
AIR ($\mu\text{U} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$)	796.3 (678.6–934.5)	953.4 (897.8–1,012.3)	0.049
Disposition index†	3,071 (2,416.3–3,904.9)	3,714 (3,361.0–4,105.2)	0.18
HDL cholesterol (mg/dl)	41.3 (37.7–45.2)	42.1 (40.9–44.3)	0.61
Triglycerides (mg/dl)	59.7 (48.9–73.0)	53.0 (48.4–58.0)	0.30

Data are percentages of demographic characteristics at baseline (first visit). Other data are means (95% CI) in original scales adjusted for age, Tanner stage, ethnicity, and gender using linear random-effects models (PROC MIXED in SAS, version 8.1, SAS Institute, Cary, NC). The differences of means between two groups that reached statistical significance level at $\alpha = 0.05$ are shown in bold; †Disposition index was estimated by $S_i \times \text{AIR}$.

RESULTS

Demographic and overall metabolic characteristics

At the first visit, the total sample comprised 38.9% boys and 61.9% Caucasians; at this point, most of the children were in Tanner stage 1 (92.8%). The LBW group had a mean birth weight of 1.95 ± 0.2 kg, and the NBW group had a mean birth weight of 3.6 ± 0.1 kg. There were no significant differences in sex, ethnicity, average age, and average weight between LBW and NBW children; however, LBW children were lower in stature, had higher fasting insulin, and had a lower AIR, as summarized in Table 1.

Effects of LBW on the components of IRS by ethnicity

Fasting insulin

Average fasting insulin level across full birth weight range was $12.7 \mu\text{U}/\text{dl}$ with a 95% CI of 11.9–13.5 $\mu\text{U}/\text{dl}$. Among African-American children, LBW was significantly associated with higher fasting insulin. Among children with LBW, the fasting insulin was significantly higher in African-Americans than Caucasians (Fig. 1A).

S_i

Average S_i level across full birth weight range was $4.01 \times 10^{-5} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{dl}^{-1}$ with a 95% CI of $3.70\text{--}4.44 \times 10^{-5} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{dl}^{-1}$. S_i was significantly lower among African-American children than among Caucasian children ($P < 0.01$), regardless of birth weight (Fig. 1B).

AIR

The average AIR level across full birth weight range was $871.3 \mu\text{U} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$ with a 95% CI of $800.9\text{--}947.9 \mu\text{U} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$. Among African-American children, LBW was significantly related to a lower AIR ($P < 0.01$). Among children with NBW, African-Americans had higher AIR concentration than Caucasians ($P < 0.001$; Fig. 1C).

Disposition index

The disposition index was lower in both Caucasian and African-American children with LBW than those with NBW, although this difference did not reach statistical significance ($P > 0.05$). However, among children with NBW, African-American children showed a significantly higher disposition index than Caucasian children ($P < 0.001$; Fig. 1D).

Visceral fat

Average visceral fat across full birth weight range was 31.2 cm^2 with a 95% CI of $26.7\text{--}36.7 \text{ cm}^2$. LBW was significantly associated with greater visceral fat among African-American children ($P < 0.05$), but not among Caucasian children. In children with NBW, African-Americans had a significantly lower visceral fat level than Caucasians ($P < 0.01$; Fig. 1E).

HDL cholesterol

Average HDL cholesterol level across full birth weight range was $41.7 \text{ mg}/\text{dl}$ with a 95% CI of $39.3\text{--}44.8 \text{ mg}/\text{dl}$. Among African-American children, LBW was significantly associated with lower HDL cholesterol than NBW ($P < 0.05$; Fig. 1F).

Interaction between LBW and ethnicity on the components of IRS

The significant interaction between LBW and ethnicity was detected for fasting insulin ($P < 0.05$) and visceral fat mass ($P = 0.05$), indicating that the effects of LBW on fasting insulin and visceral fat were more pronounced in African-American children (Fig. 1, Table 2).

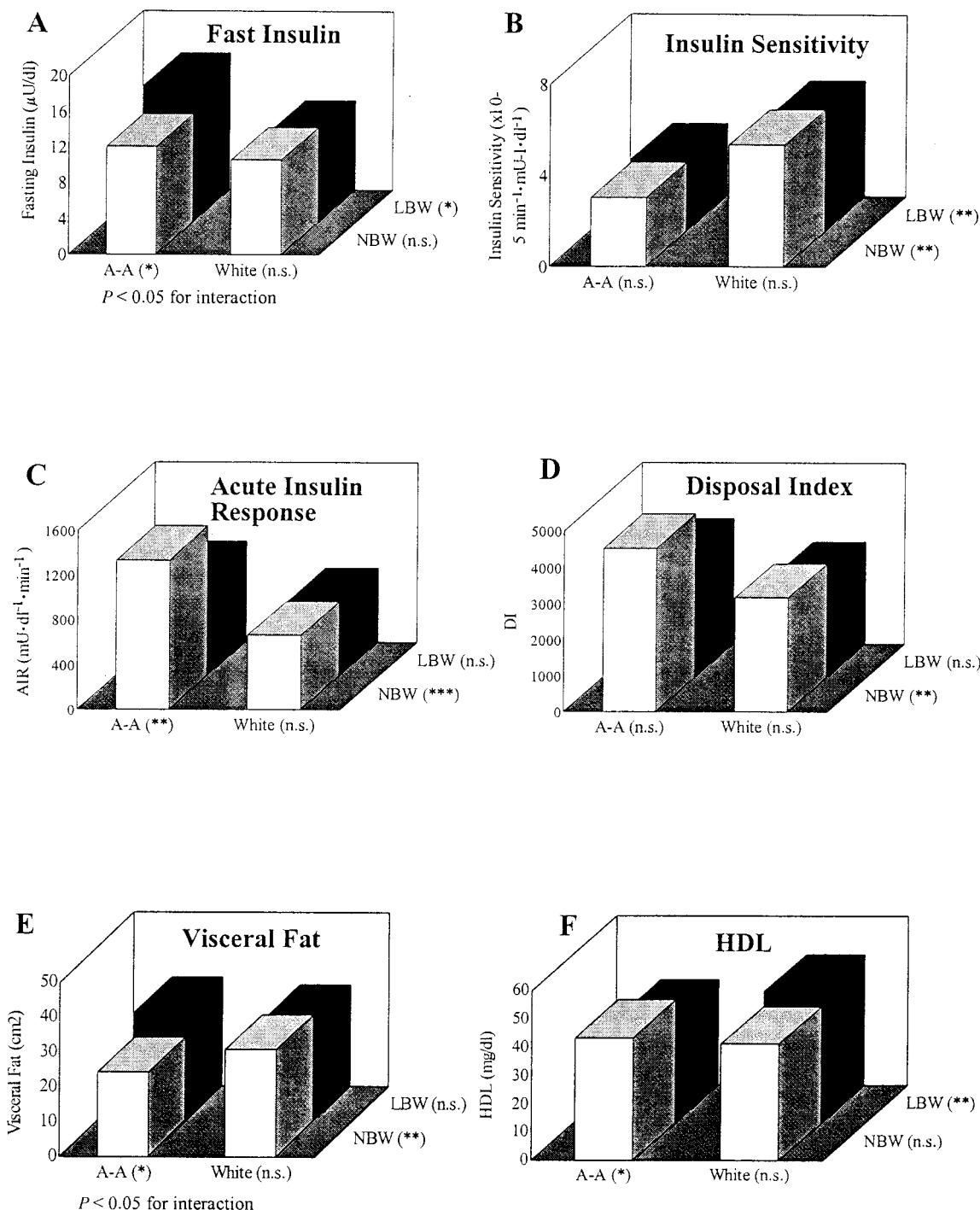


Figure 1—Mean levels of IRS components by ethnicity and birth weight. Data were adjusted for age, Tanner stage, sex, and total fat mass. A: Fasting insulin; B: S_i ; C: AIR; D: disposition index; E: visceral fat; F: HDL cholesterol. A-A, African-American; n.s., not significant. * $P < 0.05$; ** $P < 0.01$.

Effects of LBW on developmental trends of the components of IRS over age

The regression coefficients of the interaction term between LBW and age in Table 2 reflected the effects of LBW on the developmental trends of outcome variables.

The results showed that LBW was associated with a significantly lower age-related decrement of AIR ($P < 0.05$) and the disposition index as a marker of β -cell-function ($P < 0.01$), but higher age-related increment of triglycerides ($P < 0.01$).

Effects of LBW on the hyperbolic function between S_i and AIR

The regression coefficient of the interaction term between LBW and S_i in Table 2 indicates the effect of LBW on the slope of AIR regressed on S_i . The data showed that hyperbolic function between S_i and AIR

Table 2—Fixed effects from the linear random-effects models for fasting insulin, AIR, S_i , disposal index, and triglyceride

Effect [¶]	Fasting insulin ($\mu\text{U}/\text{dl}$, ln)	AIR ($\mu\text{U} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$, ln)	S_i ($\times 10^{-5} \text{ min}^{-1} \cdot \text{U}^{-1} \cdot \text{dl}$, ln)	Disposition index (ln)	Triglycerides (mg/dl, ln)
Intercept	2.40 (0.06) [§]	7.3 (0.08) [§]	1.18 (0.10) [§]	8.42 (0.10) [§]	3.76 (0.08) [§]
Age (years)	0.001 (0.02)	-0.09 (0.02) [§]	1.01 (0.02)	-0.06 (0.03) [†]	0.001 (0.02)
LBW (kg)	0.25 (0.11) [†]	-0.38 (0.15) [†]	0.05 (0.17)	-0.22 (0.19)	0.21 (0.12) [*]
Ethnicity	-0.12 (0.06) [†]	-0.77 (0.09) [§]	0.59 (0.09) [§]	-0.37 (0.10) [§]	0.33 (0.08) [§]
Gender	0.02 (0.05)	0.13 (0.07) [*]	0.10 (0.08)	0.23 (0.09) [‡]	-0.10 (0.07)
Tanner stage	0.11 (0.03) [§]	0.01 (0.05)	-0.10 (0.06) [*]	-0.02 (0.06)	0.12 (0.05) [†]
Total fat mass (kg)	0.40 (0.04) [§]	0.14 (0.06) [†]	-0.51 (0.06) [§]	-0.25 (0.07) [‡]	0.17 (0.05) [‡]
S_i	—	-0.35 (0.05) [§]	—	—	—
LBW \times ethnicity	-0.28 (0.13) [†]	1.25 (0.24)	-0.21 (0.21)	-0.09 (0.27)	-0.09 (0.19)
LBW \times age	-0.03 (0.03)	0.08 (0.04) [†]	0.07 (0.05)	0.10 (0.05) [†]	0.08 (0.03) [‡]
LBW \times Tanner	0.01 (0.02)	0.001 (0.03)	-0.03 (0.03)	0.65 (0.52)	0.03 (0.03)
LBW \times S_i	—	0.28 (0.13) [†]	—	—	—

Data are β (SEM). * $P < 0.10$; † $P < 0.05$; ‡ $P < 0.01$; § $P < 0.001$; ||disposal index was calculated by the formula of ($S_i \times \text{AIR}$) as an estimate of β -cell function; ¶random effects (between- and within-subject variances/covariances) were not shown in this table (available from the first author upon request). Conditional linear growth curve models were constructed to estimate the effects of age (continuous), birth weight (1 = LBW, 0 = NBW), ethnicity (1 = Caucasian, 0 = African-American), and covariates on fasting insulin, AIR, S_i , disposal index, and triglycerides. Age, total fat, and S_i were centralized at their grand mean levels (i.e., original scores subtracted from the grand means) in the models to facilitate interpretations of the intercept and to avoid possible colinearity.

was retarded among children with LBW ($P = 0.04$; Fig. 2).

Association among puberty, LBW, and the components of IRS

More than 90% of both LBW and NBW children were in prepuberty at the start of the study (Table 1). LBW was not related to either the average Tanner stages or the transition across stages. However, faster transition of Tanner stages over age was examined in African-American as compared with Caucasian children ($\beta = 0.50$, $P < 0.0001$ vs. $\beta = 0.25$, $P < 0.0001$; $\gamma = 0.13$, $P < 0.001$ for testing the differences between the two slopes). Tanner stage was significantly associated with a higher level of fasting insulin, systolic blood pressure, and triglycerides and was marginally associated with lower insulin sensitivity. No interaction between Tanner stage and LBW on the components of IRS was identified (Table 2).

CONCLUSIONS—The present study tested the differential effects of LBW on the components of IRS in Caucasian and African-American children and examined the effects of LBW on the developmental trends of certain components of IRS in relation to age and total fat mass using a longitudinal random-effects modeling approach. The results showed that 1) LBW was significantly associated with increased fasting insulin concentration, visceral fat mass, triglycerides, decreased AIR, β -cell function, and HDL cholesterol

among African-American children; 2) among children with LBW, there were significant differences in fasting insulin, S_i , AIR, and HDL cholesterol between Caucasians and African-Americans; 3) interactions between LBW and ethnicity on fasting insulin concentration and visceral fat were statistically significant; 4) LBW was associated with a more rapidly de-

creasing AIR and increasing triglyceride levels with regard to age; 5) the hyperbolic function between S_i and β -cell function was retarded among children with LBW; and 6) no significant associations between LBW and fasting glucose concentration, S_i , and systolic blood pressure were detected among both Caucasians and African-Americans in this study.

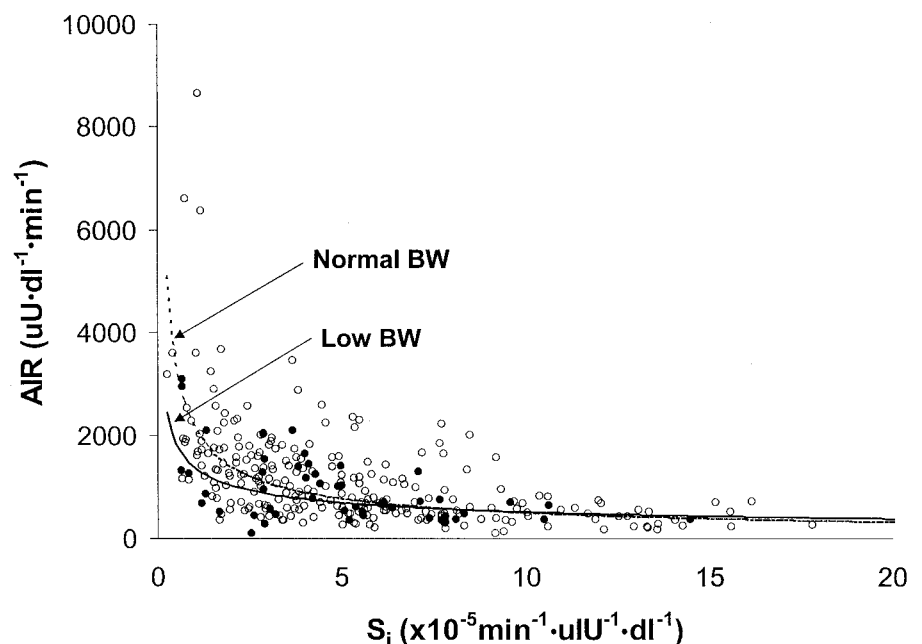


Figure 2—Hyperbola relation between S_i and AIR by birth weight on the original scale. There were 560 observations of 139 subjects. The slopes of two linear lines with log-transformed scale were significantly different ($P = 0.04$). Data were adjusted for age, Tanner stage, ethnicity, sex, and total fat mass. \circ , Normal birth weight; \bullet , low birth weight. BW, birth weight.

The finding in our longitudinal study that LBW was significantly related to fasting insulin in African-American children was consistent with findings in India (12,13), Britain (14,15), the U.S. (16), and South Africa (17). The lack of an association between LBW and fasting glucose in both Caucasian and African-American children was similar to those in Britain (14,15) but was in contrast to those in India (12,13) and South Africa (17). The U-shaped relation between the categorical scale of birth weight and 2-h glucose concentration, as observed in Pima Indians in the U.S. (16), may provide some information that the average glucose concentration would be quite similar when birth weight was dichotomized as LBW (<2,500 g) and NBW (\geq 2,500 g) as in our study. Despite the lack of association with fasting glucose, LBW was significantly related to elevated fasting insulin, a consistent marker of insulin resistance in normoglycemic individuals (1). Furthermore, this relation was quite stable over age after adjusted for total body fat mass (data not presented), which provided evidence that fetal malnutrition leads to permanent alterations in structure and function of endocrine pancreas such as elevated insulin concentration and reduced β -cell mass, as proposed in the “thrifty phenotype hypothesis” (29).

The significant association between LBW and decreased β -cell function determined in our study provided further evidence that retarded fetal growth may result in a reduced number of pancreatic β -cells and, therefore, a reduced capacity of producing insulin (29). The well-known hyperbolic relationship between S_i and AIR is based on an increase in AIR in response to a reduction in S_i (30). However, as also shown in Fig. 2, the increase in AIR in response to decreased S_i is repressed among children with LBW, suggesting impairment in β -cell response among children with LBW. Animal experiments have shown that the offspring of rats fed an isocaloric, low-protein diet during pregnancy have reduced birth weight, islet size, and vascularization (31) as well as impaired insulin secretion (32). Our study provided first evidence for the association between LBW, as a marker of poor fetal nutrition, and impaired β -cell function in human subjects.

No previous studies have examined the associations between LBW and ab-

dominal obesity and dyslipidemia in children in the context of IRS. In contrast with one of the past studies in adults (3), we found that LBW was significantly related to increased visceral fat mass. In our past studies, visceral fat was independently associated with elevated triglycerides and insulin (19,20). In the present study, we found that it was unlikely that increased visceral fat caused elevated fasting insulin in children, because LBW was significantly associated with both elevated fasting insulin and visceral fat. Instead, our study provided some evidence that the effect of LBW on fasting insulin may be mediated through visceral fat. Consistent with previous studies in adults (2,6) and children (33), LBW was significantly associated with reduced HDL cholesterol level and marginally associated with elevated triglycerides in African-American children, even after adjusted for total body fat. Moreover, the progression of triglycerides over age was more rapid among children with LBW than those with NBW. Although the mechanism linking LBW and dyslipidemia is unknown, our findings seem to support the suggestion that impaired growth of the fetal liver in utero may lead to permanent changes in lipid metabolism (34).

The lack of an association between LBW and glucose intolerance, S_i , and systolic blood pressure was in contrast with recent studies in young adults (9,10,35) and, therefore, provided little evidence in supporting the suggestion that intrauterine programming of the hypothalamic-pituitary-adrenal axis may be a functional mechanism underlying the association between LBW and the IRS (9,36). However, there were significant differences in fasting insulin, S_i , AIR, and HDL cholesterol between Caucasian and African-American children with LBW, and the interaction between LBW and ethnicity on fasting insulin and visceral fat was significant as determined in our study, suggesting that the genetic and environmental influence on insulin resistance may be more manifest during childhood (8,10,19,37,38).

Puberty was not related to LBW in our study; however, it was significantly associated with higher levels of fasting insulin and triglycerides and marginally associated with lower S_i . This finding was consistent with recent studies in which precocious pubarche was found to be associated with hyperinsulinemia (39) and

puberty was related to insulin resistance (40). In particular, more rapid transition between Tanner stages as identified in African-Americans may explain, at least in part, the more pronounced effects of LBW on the components of the IRS in this population.

A limitation of our study was the lack of information for gestation at birth; therefore, we were unable to distinguish children with normal gestation time from those with premature delivery. Fortunately, the interpretation of our findings might not be affected by this limitation, because previous studies have shown that the effect of LBW on insulin resistance was independent of duration of gestation (2,14). However, our study might underestimate the association between LBW and the components of IRS, because past studies showed that inclusion of preterm births could obscure the relation of birth weight with metabolic variables (3). Another weakness of this study was attributable to the dearth of validation of parental recall of birth weight. However, several previous studies have suggested that recalled birth weights are sufficiently accurate for use in children \leq 16 years of age, regardless of socioeconomic status (41). Whincup et al. (15) found that the strength of the relation between insulin and birth weight from birth record data were very similar to those obtained from maternal recall.

Despite these limitations, there are at least three unique strengths in our study. First, a longitudinal design made it possible to observe the individual changes of physical and plasma measurements over age and to improve the study power (18,42). Second, this study used advanced measurement techniques for accurate clinical assessment of insulin action and secretion and body composition and fat distribution. Finally, associations between LBW and major components of the IRS were examined thoroughly, and to our knowledge, some of these associations were identified for the first time in African-American children.

In conclusion, the present study indicated that LBW was associated with an increased risk of IRS among children aged 4–14 years. African-American children with LBW were at the highest risk of developing IRS during childhood. The findings suggest that hyperinsulinemia, decreased β -cell function, dyslipidemia,

and central obesity, which are associated with LBW, might be the first components of IRS during childhood. More follow-up is necessary to establish whether and when other symptoms develop in young adulthood and later life.

Acknowledgments—This study was supported by the U.S. Department of Agriculture (M.I.G.), the National Institute of Child Health and Development (M.I.G., Grants R29-HD-32668 and R01-HD/HL-33064), and by General Clinical Research Center Grant M01-RR-00032.

We thank Rey Figueroa for physician coverage, Barbara Gower for insulin and minimal model analysis, Tena Hilario for coordination of this project, the staff of the General Clinical Research Center, and the children and families who participated in this study.

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