Relation of Birth Weight to Fasting Insulin, Insulin Resistance, and Body Size in Adolescence

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OBJECTIVE — A relationship between birth weight and the insulin resistance syndrome has been reported in adults but has not been defined in adolescents.

RESEARCH DESIGN AND METHODS — Data were analyzed in 296 children (132 girls and 164 boys) mean age 15.0 ± 1.2 years who had euglycemic insulin clamp studies (intravenous administration of 1 mU · kg^{-1} · min^{-1} of insulin balanced by a variable infusion of 20% glucose to maintain blood glucose at 100 mg/dl). Insulin sensitivity (M_{LBM}) was determined by glucose uptake per kg lean body mass (LBM), and parents reported birth weight.

RESULTS — Birth weight ranged from 1,021 to 4,848 g (mean ± SD 3,433 ± 551), with 4.0% <2,500 g. Fat mass and BMI had U-shaped relations with birth weight after adjustment for race, age, sex, and blood pressure. Lean mass index (lean mass/height squared) was stable across birth weight quartiles. Fasting insulin decreased nonsignificantly across birth weight quartiles but became significant after adjustment for adolescent weight ($P = 0.008$). Although M_{LBM} was highest in the highest birth weight quartile, the pattern was not significant. Triglycerides tended to increase with birth weight, whereas LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) tended to decrease. Blood pressure was unrelated to birth weight.

CONCLUSIONS — In this cohort, fat mass was greater in adolescents with low and high birth weight; fasting insulin was lower with higher birth weight after adjustment for adolescent weight. Insulin sensitivity increased nonsignificantly with birth weight.

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Low (1–5) and high (6) birth weight are both associated with an increased risk for type 2 diabetes and cardiovascular disease in adults. The relationship of birth weight to these diseases is thought to represent the influence of fetal nutrition on the prenatal programming of processes that effect long-term growth and metabolism (7,8). Studies in children and adolescents from different cultures suggest that an association between birth weight and the insulin resistance syndrome also can be identified early in life (9–11).

Previous studies in children have used fasting and postload glucose and insulin to relate birth weight to estimates of β-cell insulin production and insulin resistance (9–11). However, serum and plasma insulin and glucose levels represent an integrated response to secretion, metabolism, and clearance of insulin and glucose, and it is generally agreed that the hyperinsulinemic-euglycemic clamp is a more accurate measure of insulin resistance (12). In the present study, the relationship of birth weight to factors associated with the insulin resistance syndrome was examined in adolescents who had hyperinsulinemic-euglycemic clamps performed as part of a longitudinal study on cardiovascular risk.

RESEARCH DESIGN AND METHODS

— This study was approved by the Institutional Review Board: Human Subjects Committee of the University of Minnesota. Written consent was obtained from all children and their parents/guardians.

The children participating in this study were recruited after a blood pressure screening of 12,043 5th- through 8th-grade Minneapolis Public School students. This sample represents 93% of all eligible students in those grades. Recruitment letters were mailed to 2,915 randomly selected black and non-Hispanic white children with stratification according to sex- and race-specific systolic blood pressure percentile (half from the upper 25 percentiles and half from the lower 75 percentiles to enrich the study population with potentially higher-risk children). Of these, 537 attended an information meeting (held in groups of 20–30 children and their parents) where the study was explained in detail and an incentive of $75 was offered for participation. A total of 401 participants gave informed consent. The present cohort consists of the 296 children who completed an insulin clamp study at mean age 15 years (range 13–17), 2 years after completing a clamp at baseline. There were no significant differences in blood pressure, height, and weight (the only measurements made during the school screening examination) between this cohort and the 2,915 randomly selected children, the 537 who attended the information session, or the 401 who provided informed consent. The participants included in the current analyses were more likely to be black (40 vs. 21% black, $P = 0.0003$) and have higher birth weight (3,268 vs. 3,421 g, $P = 0.03$).

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Abbreviations: HDL-C, HDL cholesterol; HOMA estimate, homeostasis model to estimate insulin resistance; LBM, lean body mass; LDL-C, LDL cholesterol.

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

Table 1—*Anthropometric and physiological characteristics for boys and girls* (*N* = 296)

Variable	Boys	Girls	*P**	Black	White	*P*
n						
Black	37	17				
White	127	115	0.03			
Birth data						
Birth weight (g)	3,484 ± 47	3,371 ± 42	0.07	3,259 ± 60	3,473 ± 36	0.003
Birth length (cm)	52.3 ± 0.3	51.8 ± 0.2	0.1	52.2 ± 0.5	52.1 ± 0.2	0.8
Ponderal index (kg/m^3)	24.3 ± 0.3	24.2 ± 0.3	0.8	23.3 ± 0.5	24.5 ± 0.23	0.11
Adolescent data						
Age at clinic (years)	15.0 ± 0.1	14.9 ± 0.1	0.2	14.4 ± 0.2	14.9 ± 0.1	0.05
Tanner Stage	4.5 ± 0.1	4.6 ± 0.1	0.6	4.3 ± 0.1	3.9 ± 0.1	0.0006
Height (cm)	174.2 ± 0.6	164.6 ± 0.6	<0.0001	169.3 ± 0.1	170.1 ± 0.5	0.5
Weight (kg)	71.1 ± 1.3	64.5 ± 1.4	0.0007	68.5 ± 2.2	68.1 ± 1.0	0.9
LBM (kg)	48.8 ± 0.6	40.1 ± 0.6	<0.0001	46.1 ± 1.0	44.6 ± 0.5	0.2
Fat mass (kg)	22.3 ± 1.3	24.4 ± 1.5	0.3	22.3 ± 1.3	23.4 ± 1.5	0.7
BMI (kg/m^2)	23.3 ± 0.4	23.8 ± 0.4	0.6	23.9 ± 0.7	23.4 ± 0.3	0.5
LMI (kg/m^2)	16.0 ± 0.2	14.8 ± 0.2	<0.0001	15.9 ± 0.3	15.4 ± 0.1	0.05
FMI (kg/m^2)	7.3 ± 0.4	9 ± 0.5	0.01	7.9 ± 0.8	8.1 ± 0.4	0.8
Systolic BP	111.4 ± 0.6	105.4 ± 0.7	<0.0001	110.3 ± 1.1	108.3 ± 0.5	0.1
Diastolic BP	54.3 ± 1.1	59.6 ± 1.2	0.001	58.5 ± 1.9	56.3 ± 0.8	0.3
Laboratory data						
Insulin (mU/l)	15.3 ± 0.7	15.1 ± 0.8	0.8	15.5 ± 1.3	15.2 ± 0.6	0.8
M_{LBM} (mg · kg LBM^{-1} · min^{-1})	12.8 ± 0.3	11.7 ± 0.4	0.05	12.4 ± 0.6	12.3 ± 0.3	0.9
Cholesterol (mmol/l)	3.8 ± 0.06	3.8 ± 0.06	0.8	3.8 ± 0.1	3.8 ± 0.05	0.6
HDL-C (mmol/l)	1.2 ± 0.02	1.1 ± 0.02	0.003	1.2 ± 0.03	1.1 ± 0.02	0.02
LDL-C (mmol/l)	2.2 ± 0.06	2.2 ± 0.05	0.9	2.2 ± 0.05	2.2 ± 0.05	0.8
Triglycerides (mmol/l)	1.03 ± 0.04	0.89 ± 0.04	0.03	0.8 ± 0.07	1.0 ± 0.03	0.01

Data are means ± SE unless otherwise indicated. Birth data, race, tanner stage, and age are unadjusted means. Other values are adjusted by linear regression for age, sex, Tanner stage, race, and screening blood pressure strata. **P* for F-test. BP, blood pressure; FMI, fat mass index; LBM, lean body mass; LMI, lean mass index.

Birth weight and length were reported by the parents of the participants. Validity of parent-reported birth weight has been previously confirmed (13,14). Tanner staging was completed during a complete physical examination by a pediatrician. Anthropometric measurements were made with participants in study gowns and without shoes. Height was measured using a wall-mounted stadiometer. Weight was measured using a balance scale. Waist and hip circumferences were measured to the nearest 0.5 cm. The mean of two triceps and subscapular skinfold measurements was used in the analyses. Lean body mass (LBM), i.e., fat-free mass, was calculated by the method of Slaughter (15), based on skinfold measurements, sex, race, and Tanner stage. To assess the relative weight for height, we calculated BMI as kilograms per meters squared. We computed indexes parallel to BMI for lean mass and fat mass (kilograms lean mass/meters squared and kilograms fat mass/meters squared). The measures fat mass, percent body fat, and fat mass index provide highly overlapping information ($r > 0.95$ for each pair). The lean mass index was presented because it was the only measure of lean mass that accounted for height. For consistency with BMI, we present the fat mass index as well as the lean index and omitted specific mention of the percent body fat. Blood pressure was determined from the average of two blood pressure measures (systolic and fifth-phase Korotkoff diastolic) taken twice on the right arm using a random-zero sphygmomanometer with subjects in the seated position.

The euglycemic insulin clamp studies were conducted in the University of Minnesota Clinical Research Center. Participants were admitted after a 10-h overnight fast. An intravenous catheter was inserted into an arm vein 1 h before the clamp studies, and a blood sample was obtained immediately for measurement of serum lipids. This catheter was used for infusion of potassium phosphate, insulin, and glucose. A contralateral vein was cannulated for blood sampling, and the hand was placed in a heated box (65°C) to arterialize venous blood for measurement of glucose levels. Insulin was infused at a rate of 1 mU · kg^{-1} · min^{-1} for 3 h. A variable infusion of 20% glucose was adjusted based on plasma glucose levels measured every 5 min to maintain euglycemia, i.e., plasma glucose at 100 mg/dl (5.6 mmol/l). Insulin sensitivity (M) was determined from the amount of glucose required to maintain euglycemia over the final 40 min of the euglycemic clamp study and was expressed as M_{LBM} (milligrams per kilograms of LBM per min) for whole-body glucose utilization.

Plasma glucose was measured immediately at the bedside with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Blood samples for serum insulin levels were obtained at baseline (–5 and 0 min before starting the insulin infusion). The samples were collected on ice and centrifuged within 20 min. Insulin levels were measured in the Fairview-University Medical Center laboratory using a radioimmunoassay kit.

Table 2—*Anthropometric and physiological characteristics by birth weight quartile*

	Birth weight quartile				
	1	2	3	4	*P
n					
Boys	35	38	40	51	
Girls	36	40	33	23	
Black	20	14	12	8	
White	51	64	61	66	
Birth data					
Birthweight (g)	2,730 ± 29	3,266 ± 28	3,635 ± 29	4,087 ± 29	
Birth length (cm)	49.9 ± 0.3	51.4 ± 0.3	52.8 ± 0.3	54.4 ± 0.3	
Ponderal index (kg/m^3/1000)	22.1 ± 0.4	24.4 ± 0.4	24.9 ± 0.4	25.6 ± 0.4	
Adolescent data					
Age at clinic (years)	14.8 ± 1.2	15.0 ± 1.3	15.0 ± 1.3	15.0 ± 1.2	
Height (cm)	167.4 ± 0.8	168.2 ± 0.7	170.6 ± 0.8	173.7 ± 0.8	<0.0001
Weight (kg)	66.8 ± 1.9	63.2 ± 1.8	70.11 ± 1.8	72.6 ± 1.9	0.004
LBM (kg)	43.6 ± 0.8	44.3 ± .8	45.4 ± 0.9	46.3 ± 0.9	0.02
Fat mass (kg)	23.2 ± 1.9	19.0 ± 1.8	24.7 ± 1.9	26.3 ± 1.8	0.09
BMI (kg/m^2)	23.7 ± 0.6	22.3 ± 0.5	24.1 ± 0.6	24.1 ± 0.6	0.3
Lean mass index (kg/m^2)	15.5 ± .3	15.6 ± 0.2	15.5 ± 0.3	15.3 ± 0.3	0.6
Fat mass index (kg/m^2)	8.2 ± 0.6	6.7 ± 0.6	8.6 ± 0.6	8.7 ± 0.6	0.2
Waist circumference (cm)	80.6 ± 1.5	77.2 ± 1.4	81.1 ± 1.5	81.8 ± 1.5	0.2
Subscapular skinfold (mm)	17.6 ± 1.2	14.4 ± 1.1	17.7 ± 1.1	18.6 ± 1.2	0.2
Systolic BP (sitting)	109.1 ± 0.9	107.2 ± 0.9	109.2 ± 0.9	109.5 ± 0.9	0.4
Diastolic BP (sitting)	56.2 ± 1.6	56.1 ± 1.6	56.4 ± 1.6	58.2 ± 1.6	0.4
HDL-C (mmol/l)	1.1 ± 0.03	1.2 ± 0.03	1.1 ± 0.03	1.1 ± 0.03	0.2
Triglyceride (mmol/l)	0.93 ± 0.06	0.94 ± 0.06	0.98 ± 0.06	1.02 ± 0.06	0.7
LDL-C (mmol/l)	2.3 ± 0.08	2.2 ± 0.07	2.1 ± 0.08	2.2 ± 0.08	0.5

Data are means ± SE unless otherwise indicated. Birth data are unadjusted. Data measured during adolescence are adjusted by linear regression for age, Tanner stage, sex, ethnicity, and screening blood pressure strata, except for age, which is adjusted for Tanner stage, sex, ethnicity, and screening blood pressure strata. BP, blood pressure. **P* for the linear trend across the four categories of birth weight.

Cross-reactivity was 20% with proinsulin and split products and was 0% with C-peptide. The average of the two baseline measurements was used in the analyses. Blood samples for fasting serum lipids were analyzed in the Fairview-University Medical Center laboratory using a Cobas FARA. Cholesterol was determined by a standard enzymatic-cholesterol oxidase-based method; HDL cholesterol (HDL-C) was determined after precipitation of non-HDL lipoproteins with magnesium/dextran precipitating reagent; triglycerides were determined using a standard glycerol blanked, enzymatic, triglyceride method. LDL cholesterol (LDL-C) was calculated by the Friedewald equation.

All analyses were conducted using SAS version 8.1, (SAS Institutes, Cary, NC). Multiple linear regression was used to assess the relationship of birth weight quartile to risk factors as dependent variables, as well as to adjust for potential confounders. All models were at least minimally adjusted for age, Tanner stage, screening blood pressure strata, and race and were sex adjusted. Further adjustments were made for *1*) weight, *2*) BMI, or *3*) lean mass index, fat mass index, and height simultaneously.

RESULTS — The characteristics of the study population are listed by sex and race in Table 1; 82% were white and 55% were male. The birth weight ranged from 1,021 to 4,848 g (mean 3,403 ± 573) with 4% of birth weights <2,500 g. Boys weighed more than girls at birth (P = 0.07). Blacks weighed less at birth than whites (P = 0.003), and weight for length (kilograms per meters cubed) was nonsignificantly lower in blacks. At average age 15 years, the boys were taller (P < 0.0001) and heavier (P = 0.002) with greater lean BMI (P < 0.0001) and lower fat mass index (P = 0.01) than girls, but they had similar BMI compared with girls. Systolic blood pressure was higher (P < 0.0001) and diastolic blood pressure was lower (P = 0.001) in boys than girls. M_{LBM} was greater in boys (P = 0.05), but fasting insulin was not different between sexes. HDL-C and triglycerides were higher in boys than in girls. HDL-C was higher in blacks than whites (P = 0.004), and triglycerides were lower in blacks than whites (P = 0.01).

Birth weight was related to adolescent body size (Table 2). Height increased with birth weight quartile (P for linear trend = 0.001). Weight decreased nonsignificantly from the first to the second quartile and then increased significantly to the fourth quartile. BMI decreased from the first quartile to the second and then increased to the fourth quartile; it was significantly lower in the second quartile than the third and fourth quartiles (P = 0.04 and 0.03, respectively, Fig. 1). Fat mass index (Fig. 1), fat mass, waist circumference, and subscapular skinfolds (all Table 2) followed a similar pattern. Lean mass increased significantly across quartiles (Table 2, P for linear trend =

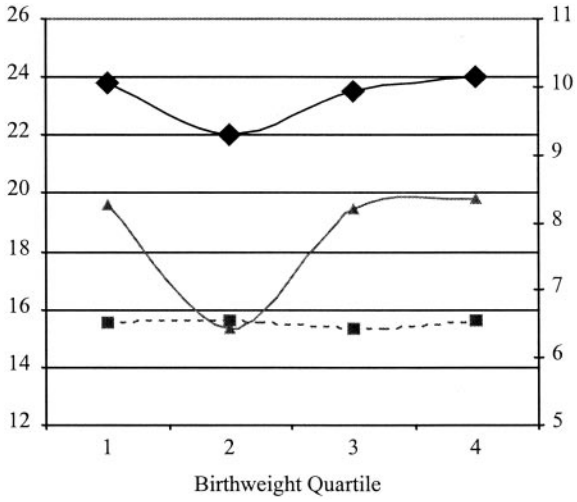

Figure 1—*Means of BMI (—◆ —), fat mass index (—▲ —), and lean mass index (---■---) according to birth weight quartile, adjusted for race, age, Tanner stage, sex, and screening blood pressure group.*

0.02), but lean mass index did not differ by birth weight quartile (Fig. 1). The patterns of height, weight, and body composition across birth weight quartiles were similar in boys and girls (data not shown).

Serum lipids and blood pressure were not different among birth weight quartiles in either sex-adjusted (Table 2) or sex-specific analyses (data not shown). Adjustments for current weight, lean and fat mass indexes, and height did not change these relationships.

Fasting insulin adjusted for race, sex, Tanner stage, and screening blood pressure stratum was lowest in the second quartile (Table 3). Adjustment of fasting insulin for adolescent body weight yielded lower insulin levels at the higher birth weight quartiles and a significant downward trend in insulin across birth weight quartiles ($P = 0.008$, Table 3 and Fig. 2). Although other body measurements were also higher in the higher birth weight quartiles, adjusting for BMI or simultaneously for lean mass index, fat mass indexes, and height (the latter not shown) only slightly increased fasting insulin in the highest quartile, and the decrease across quartiles was not (10) significant. No significant differences were found in M_{LBM} across quartiles, although M_{LBM} was highest in the highest quartile of birth weight (Table 3, Fig. 2). Adjustment for adolescent weight (Fig. 2), BMI, or simultaneous adjustment for lean mass index, fat mass index, and height (Table 3, the latter adjustment not shown) did not substantially change the relationship of birth weight to M_{LBM}.

CONCLUSIONS — In the present study, low birth weight is associated with higher insulin levels in adolescence, and the effect is independent of current adolescent weight. Despite the modest association statistically, the difference in fasting insulin between the first and fourth quartiles of birth weight after adjusting for adolescent body weight is ~20% of the average concentration (>2 mU/l). Although the relationship of birth weight to fasting insulin has been reported to be inconsistent among younger children (9,16), the two were directly related among older children after adjustment for size at the time of insulin measurement (10,11). After adjusting for weight and height, fasting insulin was higher in Pima Indian children with both low (<2.5 kg) and high (≥4.5 kg) birth weight (11). In the present report, the relationship also was significant when adjusting for current weight but not significant when adjusting for height or for BMI. Differences in results may relate to genetic characteristics of the children, particularly the predisposition to type 2 diabetes in Pima Indians.

The reported relation between birth weight and body size in children and adolescents also is not consistent. In the present study, a U-shaped relation between birth weight and BMI, fat mass index, waist circumference, and subscapular skinfold was observed. Studies of younger children report a positive relationship between birth weight and childhood BMI (9,16) or ponderal index (10). When the relationship of birth weight to BMI in Pima Indians was examined in children and adolescents, the results were similar to ours in children aged 10–14 years but not among adolescents aged 15–19 years (11). In adults, a reduction in waist circumference (implying lower abdominal fat) with increasing birth weight is reported by some (17,18) but not others (8). Differences in the relation between birth weight and adolescent size may be related to a number of factors, including

Table 3—*Relationship of birth weight quartile to fasting insulin and M_{LBM} with and without adjustments for weight and body size*

	Birth weight quartile				
	1	2	3	4	*P
Fasting insulin (mU/l)	16.8 ± 1.1	13.5 ± 1.1	15.6 ± 1.0	15.1 ± 1.1	0.2
Fasting insulin (mU/l)†	17.2 ± 0.9	15.2 ± 0.9	15.0 ± 0.9	13.6 ± 0.9	0.008
Fasting insulin (mU/l)‡	16.6 ± 0.9	14.8 ± 0.9	15.0 ± 0.9	14.5 ± 0.9	0.3
M_{LBM} (mg · kg LBM^{-1} · min^{-1})	12.1 ± 0.5	12.1 ± 0.5	11.9 ± 0.5	13.1 ± 0.5	0.2
M_{LBM} (mg · kg LBM^{-1} · min^{-1})†	12.1 ± 0.5	12.0 ± 0.5	12.0 ± 0.5	13.2 ± 0.5	0.3
M_{LBM} (mg · kg LBM^{-1} · min^{-1})‡	12.1 ± 0.5	12.1 ± 0.5	12.0 ± 0.5	13.1 ± 0.5	0.3

Data are means ± SE. Data are adjusted by linear regression for age, Tanner stage, sex, ethnicity, screening blood pressure strata, and additional covariates as indicated. *P for the linear trend across the four categories of birth weight; †adjusted for weight; ‡adjusted for BMI.

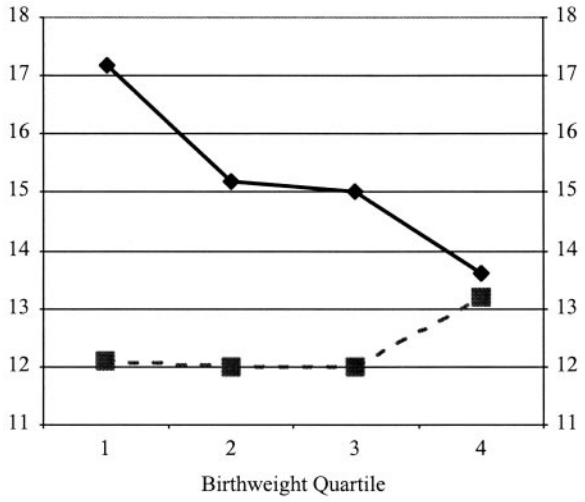

Figure 2—*Means of fasting insulin (—◆—) and M_{LBM} (---■---), adjusted for race, age, Tanner stage, sex, screening blood pressure group, and adolescent weight.*

age, ethnicity, maternal glucose tolerance during pregnancy (19,20), changing body composition in adolescence, childhood exposures to diet and physical activity, and hormonal influences such as IGF-1 (21).

The pattern of the association of birth weight to insulin sensitivity (M_{LBM}) in this study suggests greater insulin sensitivity with greater birth weight. However, the relationship was not strong. Previous studies in children and young adults using the homeostasis model to estimate insulin resistance (HOMA estimate) report a greater association with lower birth weight after adjusting for weight or some index of body fat (9–11). Previously reported data from this study (22) indicate that the HOMA estimate of insulin resistance is closely related to fasting insulin ($r = 0.99$, $P < 0.0001$) but less strongly related to M_{LBM} ($r = 0.42$, $P < 0.0001$). Therefore, the apparent difference between these results and results reported in the literature might be related to the difference between the fasting insulin or HOMA estimate and the direct measurement of insulin sensitivity from the hyperinsulinemic-euglycemic clamp.

Several studies used the hyperinsulinemic-euglycemic clamp to demonstrate an inverse (4,23) or J-shaped (24) relation of birth weight to insulin resistance in adults. This relation was independent of measures of BMI (24) and abdominal obesity (4,24). Greater insulin resistance has been found in adults born with intrauterine growth retardation than those born with normal birth weight (3)) and in men born preterm when compared with those born at term (24). We are unable to distinguish size for gestational age in the present report. Therefore, our failure to adjust for gestational age could explain the relation of birth weight to fasting hyperinsulinemia but not to insulin resistance. Alternatively, it seems reasonable to suggest that the modest but nonsignificant insulin resistance/birth weight relation seen in these adolescents will grow stronger with aging.

Significant relations of birth weight to traditional cardiovascular risk factors (blood pressure, LDL-C, HDL-C, and triglycerides) or the insulin resistance syndrome were not observed in this study, perhaps related to the age or developmental stage of the cohort. The LDL-C finding in this study is nevertheless consistent with the relation of birth weight to LDL-C in adults (5,25). These results are also similar to the findings of a meta-analysis suggesting that an inverse relation of birth weight to systolic blood pressure is present in children and adults but is weaker in adolescents (26).

The finding in this study of higher fasting insulin, but not other cardiovascular risk factors, in children with the lowest birth weight is consistent with prior observations that hyperinsulinemia precedes the development of other cardiovascular risk factors (27). Thus, the relation between low birth weight and insulin metabolism in children may be important to understanding the mechanisms influencing early expression of cardiovascular disease.

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