Persistent hypercholesterolemia is associated with the development of obesity among girls: the Bogalusa Heart Study[1–3]

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ABSTRACT

Background: Obesity is associated with cardiovascular disease (CVD) risk factors. Cross-sectional data suggest that hypercholesterolemia is associated with the development of childhood obesity.

Objective: The objective was to assess age-related changes in relative weight and the association between relative weight and CVD risk factors in hypercholesterolemic and nonhypercholesterolemic children who were nonobese at baseline.

Design: Data on relative weight and CVD risk factors were extracted from the Bogalusa Heart Study for nonobese 5–6-y-old black and white hypercholesterolemic (LDL cholesterol > 75th percentile; $n = 58$) and nonhypercholesterolemic (LDL cholesterol < 60th percentile; $n = 215$) children (41% black, 52% girls) who were also assessed 3 and 6 y later. Changes in body mass index (BMI) and CVD risk factors were assessed as a function of age, sex, race, and cholesterol concentration.

Results: BMI increased more in the hypercholesterolemic ($n = 31$) than in the nonhypercholesterolemic ($n = 111$) girls during the 6 y of follow-up but was not significantly different between hypercholesterolemic ($n = 27$) and nonhypercholesterolemic ($n = 104$) boys aged 5–12 y. Associations between BMI and the risk factors blood pressure, insulin, and blood lipids were observed to be stronger with increasing age and, in some cases, stronger in hypercholesterolemic children and girls.

Conclusions: Hypercholesterolemia is associated with increased relative weight in girls. The increased relative weight, even at an early age, is associated with a deleterious effect on blood lipids and other CVD risk factors in hypercholesterolemic children, although the strength of these associations is sex dependent. *Am J Clin Nutr* 2002;76:730–5.

KEY WORDS Hypercholesterolemia, obesity, children, Bogalusa Heart Study, girls

INTRODUCTION

Obesity is strongly associated with other cardiovascular disease (CVD) risk factors (1–8). To explain this association, it has been postulated that obesity and higher visceral abdominal fat set off a cascade, which induces or exacerbates hyperlipidemia, hypertension, and insulin resistance (4, 5, 9–14). Furthermore, the associations among adiposity and other CVD risk factors in children seem to be age-related (eg, the associations between these risk factors are stronger in older children and adults than in younger children) (1, 15). However, most of the studies of these associations have evaluated older children, adolescents, and adults, limiting the understanding of these relations in young children. In addition, most previous studies evaluating the association between adiposity and CVD risk factors have studied obese children or children from the general population (1, 4, 15–28).

An association between adiposity and other CVD risk factors in 4–10-y-old hypercholesterolemic and nonhypercholesterolemic children was described previously (29). This cross-sectional analysis showed an age-related increase in adiposity in hypercholesterolemic children, which was not observed in nonhypercholesterolemic children. However, the cross-sectional nature of these data limits the conclusions. To further examine the potential association between hypercholesterolemia and the development of obesity in children, we evaluated longitudinal data relating to the relative weight of 5–6-y-old hypercholesterolemic and nonhypercholesterolemic children from the Bogalusa Heart Study. The associations between relative weight and other CVD risk factors were also evaluated as the children grew older.

SUBJECTS AND METHODS

Subjects

The Bogalusa Heart study is a cross-sectional and longitudinal epidemiologic study of the early natural history of arteriosclerosis, coronary atherosclerosis, and essential hypertension. Children and young adults in the semirural, biracial (black and white) community of Bogalusa, LA, were surveyed between 1973 and 1991. The surveys included school-aged children and young adults (post–high school). In the original study, 3179 children aged 5–14 y (49% girls, 37% black) completed an initial lipoprotein assessment (30). Data were extracted for black and white nonobese (ponderal index < 85th percentile at baseline) children who were 5–6-y-old at the first evaluation and who had been evaluated at the next 2 evaluation points

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3 and 6 y later (at ages 8–9 and 11–12 y, respectively). Children with age-, race-, and sex-specific elevations in LDL-cholesterol concentrations (>75th percentile) at all 3 evaluations were classified as hypercholesterolemic. Children with LDL-cholesterol concentrations persistently less than the 60th percentile were considered nonhypercholesterolemic. The extracted data included age, height, weight, blood pressure, lipid profile, and insulin and glucose concentrations. Heights, weights, blood lipid values, and blood pressure measurements were available for all children in the analysis, whereas information relating to blood glucose and insulin concentrations was available for a subsample of the group.

We obtained the consent of the parents or guardians of all children participating in the Bogalusa Heart Study. The Bogalusa Heart Study protocols were approved by the Louisiana State University Institutional Review Board.

General and anthropometric assessment

All examinations followed the same protocols described previously (30). Trained personnel collected information and samples. Subjects were instructed to fast for 12 h before the screening, and compliance was determined by interview on the morning of the examination. Blood was drawn by antecubital venipuncture to obtain serum and plasma. Height and weight were measured twice to ±0.1 cm and ±0.1 kg, respectively. Blood pressure was measured in 6 replicates by 2 randomly assigned observers on the right arm of subjects while they were in a relaxed sitting position. Systolic blood pressure was recorded at the first Korotkoff phase, and diastolic blood pressure was measured at the fourth and fifth phases. The fourth phase was used in the analyses.

Laboratory analyses

From 1973 to 1986, serum total cholesterol and triacylglycerol concentrations were measured with the use of chemical procedures on a Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY) according to the protocol developed by the Lipid Research Clinics Program (31). After 1986, these variables were determined with the use of enzymatic procedures (32, 33) on an Abbott VP instrument (Abbott Laboratories, North Chicago). Serum concentrations of VLDL, LDL, and HDL cholesterol were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (34). Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program sponsored by the Centers for Disease Control and Prevention (CDC), Atlanta. Starting in 1981, CDC-assigned quality-control samples were used to examine the bias in the laboratory analysis over time. For example, the average bias in concentrations of total cholesterol on CDC control samples ranged from −0.002 to −0.04 mmol/L (−0.1 to −1.6 mg/dL) between different cross-sectional surveys, with no consistent pattern over time within or between surveys.

Plasma immunoreactive insulin concentrations were measured with a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). From 1981 to 1986, plasma glucose concentrations were measured with a glucose analyzer (Beckman Instrument Corp, Fullerton, CA) according to a glucose oxidase (EC 1.1.3.4) method. From 1987 to 1991, plasma glucose concentrations were determined as a part of a multiple chemistry profile.

Statistical analysis

Baseline characteristics of the children were compared by using one-way analysis of variance with sex and cholesterol status and their interaction as factors in the model. To assess longitudinally the change in relative weight in the 2 groups, repeated-measures analysis of variance was used with BMI as the dependent variable and age, sex, race, and hypercholesterolemia status (hypercholesterolemia compared with nonhypercholesterolemia) as the independent variables. Age at 3 levels (5–6, 8–9, and 11–12 y) was the within-subjects factor. Hypercholesterolemia status, sex, and race were the between-group factors (each with 2 levels).

The associations between relative weight (BMI) and blood pressure, glucose, insulin, and lipid concentrations for hypercholesterolemic and nonhypercholesterolemic children were examined cross-sectionally for the 3 age groups with the use of Spearman's correlations. These associations were further assessed longitudinally with the use of SAS PROC MIXED, with BMI, cholesterol status, time (first measurement, 3 y, and 6 y follow-up), and the resultant higher interaction terms as factors. Statistical significance was defined as a P value ≤ 0.05. Analyses were completed by using SAS (35) and SPSS (36) software.

RESULTS

Nonhypercholesterolemic ($n = 215$) and hypercholesterolemic ($n = 58$) children were identified. Forty-one percent of the children were black and 52% were girls. Some characteristics of the children at baseline (5–6 y of age) are shown in **Table 1**. Triacylglycerol concentrations were significantly different between the sexes, and differences in height and in LDL-cholesterol and triacylglycerol concentrations were noted by cholesterol-status group. Hypercholesterolemic boys and girls had higher LDL-cholesterol concentrations than did nonhypercholesterolemic boys and girls, respectively.

To assess the longitudinal changes in relative weight, a repeated-measures analysis of variance was completed, with BMI as the dependent variable. Significant effects were found for the following factors: age ($P < 0.0001$), the age × sex interaction term ($P < 0.0001$), the age × hypercholesterolemic status interaction term ($P = 0.04$), and the age × sex × hypercholesterolemic status interaction term ($P = 0.01$). As shown in **Figure 1**, the hypercholesterolemic girls had a greater increase in BMI from 5 to 12 y of age than did the nonhypercholesterolemic girls. At 11–12 y of age, significantly more hypercholesterolemic girls (45.2%) than nonhypercholesterolemic girls (21.6%) were overweight (BMI > 85th percentile, $P = 0.01$; 37). Over this age range, the BMI for the hypercholesterolemic and nonhypercholesterolemic boys did not differ significantly. The relation between BMI and age, sex, and hypercholesterolemia status did not change after the adjustment for baseline triacylglycerol concentration. Similarly, the increased BMI expressed in the hypercholesterolemic girls was independent of race.

The associations between BMI and blood pressure and glucose, insulin, and lipid concentrations were initially assessed cross-sectionally with the use of Spearman's correlations at the 3 initial evaluation points (ages 5–6 y, 8–9 y, and 11–12 y) for the girls (**Table 2**) and boys (**Table 3**). The longitudinal association between these factors and BMI were assessed with the use of mixed-effect-model analysis by using SAS PROC MIXED. Age and cholesterol status were also included in this model. For the girls, BMI was significantly related to systolic and diastolic blood pressure and HDL-cholesterol and triacylglycerol concentrations

TABLE 1
Baseline characteristics of hypercholesterolemic and nonhypercholesterolemic boys and girls

	Boys		Girls	
	Hypercholesterolemic	Nonhypercholesterolemic	Hypercholesterolemic	Nonhypercholesterolemic
Age (y)	5.9 ± 0.5 [27][1]	6.1 ± 0.6 [104]	5.9 ± 0.6 [31]	6.0 ± 0.6 [111]
Percentage black (%)	48	38	39	42
Weight (kg)	20.3 ± 2.7 [27]	21.0 ± 2.5 [104]	20.4 ± 3.0 [31]	20.8 ± 3.4[111]
Height (cm)[2,3]	113.5 ± 6.6 [27]	116.2 ± 5.5 [104]	113.1 ± 6.7 [31]	115.2 ± 6.1 [111]
BMI (kg/m^2)	15.7 ± 0.7 [27]	15.6 ± 1.1 [104]	16.0 ±1.4 [31]	15.6 ± 1.5 [111]
Systolic blood pressure (mm Hg)	94.7 ± 6.2 [27]	95.0 ± 8.0 [104]	95.9 ± 8.5 [31]	94.0 ± 8.5 [111]
Diastolic blood pressure (mm Hg)	55.7 ± 5.8 [27]	57.2 ± 7.0 [104]	58.2 ± 8.2 [31]	57.8 ± 7.0 [111]
Glucose (mmol/L)	4.32 ± 0.47 [23]	4.38 ± 0.52 [82]	4.41 ± 0.63 [29]	4.23 ± 0.46 [96]
Insulin (pmol/L)	66.0 ± 42.3 [13]	45.9 ± 24.4 [36]	71.0 ± 83.2 [16]	69.6 ± 74.6 [37]
LDL cholesterol (mmol/L)[2–4]	3.28 ± 0.40 [27]	1.92 ± 0.34[2] [104]	3.60 ± 0.60 [31]	2.00 ± 0.34 [111]
Triacylglycerol (mmol/L)[2–5]	0.76 ± 0.28 [27]	0.57 ± 0.24[2] [104]	0.92 ± 0.43 [31]	0.61 ± 0.27 [111]
HDL cholesterol (mmol/L)[4]	1.58 ± 0.50 [27]	1.66 ± 0.43 [104]	1.32 ± 0.54 [31]	1.67 ± 0.44 [111]

[1] $\bar{x}$ ± SD; *n* in brackets.
[2] Significant difference between hypercholesterolemic and nonhypercholesterolemic boys, $P < 0.05$.
[3] Significant difference by cholesterol status, $P < 0.05$.
[4] Significant difference between hypercholesterolemic and nonhypercholesterolemic girls, $P < 0.05$.
[5] Significant difference between boys and girls, $P < 0.05$.

($P < 0.0001$). In addition, the relations between BMI and systolic blood pressure ($P < 0.0001$), diastolic blood pressure ($P = 0.008$), and triacylglycerol concentration ($P < 0.0001$) increased with age in the girls. The relations between BMI and systolic blood pressure ($P = 0.02$) and between BMI and triacylglycerol concentration ($P = 0.01$) were also stronger with age in the hypercholesterolemic than in the nonhypercholesterolemic girls ($P < 0.0001$). In the boys, BMI was associated with insulin concentration ($P = 0.01$) and systolic blood pressure ($P = 0.0004$). In addition, the relation between BMI and systolic blood pressure ($P = 0.01$) and diastolic blood pressure ($P = 0.0003$) changed with age in the boys; the relation between BMI and diastolic blood pressure also differed with age between the hypercholesterolemic and nonhypercholesterolemic boys ($P = 0.03$).

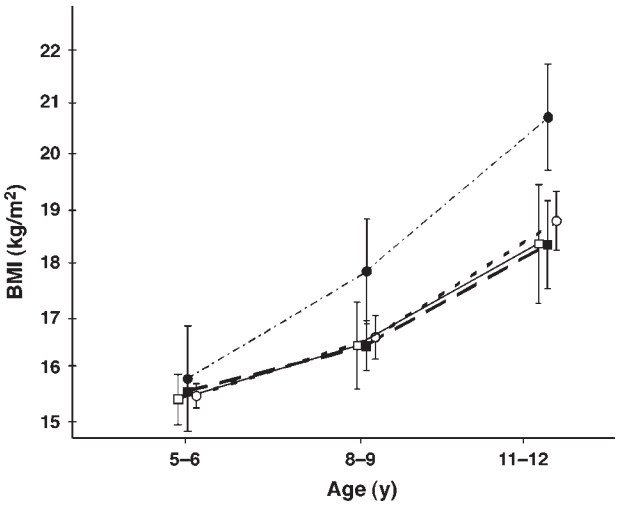

FIGURE 1. BMI as a function of age in hypercholesterolemic (●) and nonhypercholesterolemic (○) girls and hypercholesterolemic (■) and nonhypercholesterolemic (□) boys. The BMI of the hypercholesterolemic girls increased significantly with age compared with the nonhypercholesterolemic girls. No significant differences between nonhypercholesterolemic and hypercholesterolemic boys were observed

DISCUSSION

In this longitudinal assessment of changes in relative weight in young hypercholesterolemic children, we found an increase in BMI with age in the hypercholesterolemic girls. These findings contrast with those in the literature, which suggest that obesity precedes the development of dyslipidemia (4, 5, 9–14, 16). However, these current longitudinal findings are somewhat consistent with a previous assessment of cross-sectional data relating to hypercholesterolemic and nonhypercholesterolemic children, which suggests that hypercholesterolemic boys and girls developed increased adiposity between 6 and 10 y of age (29).

This previous cross-sectional analysis also showed that systolic blood pressure and insulin concentrations were positively correlated with the increased adiposity of the hypercholesterolemic children. The current longitudinal analysis showed a correlation between BMI and other CVD risk factors, but more of these relations were significant for the girls than for the boys. This is consistent with an earlier expression of obesity and CVD risk factors in girls, as indicated by the observation that, at presentation, the mean age of adolescent girls with type 2 diabetes was lower than the mean age of adolescent boys with new onset type 2 diabetes (38). It is possible that the dramatic changes in lipids and lipoproteins occurring in boys between the ages of 9 and 15 y or the differences in sex hormones and timing of onset of puberty between boys and girls may influence the sex differences observed in our analysis (39). However, such a sex difference was not observed in our previous study (29). Similarly, Bao et al (40) reported that an elevated LDL-cholesterol concentration in childhood was associated with obesity and dyslipidemia in adulthood in both sexes. Given these different results for boys and girls, an evaluation of these relations in young boys and girls that involves follow-up past the age of 12 y into adolescence should be considered. Other studies also defined ethnic differences in development and maturation, which affect body composition (41). However, the pattern of

TABLE 2
Spearman's correlation coefficients (*r*) between BMI and other cardiovascular disease risk factors for girls by age group[1]

	Girls	
	Hypercholesterolemic	Nonhypercholesterolemic
5–6 y of age		
Systolic blood pressure	0.36[2] [31]	0.30[3] [111]
Diastolic blood pressure	0.37 [31]	0.14 [111]
Glucose	0.10 [29]	0.16 [96]
Insulin	−0.06 [16]	0.15 [37]
LDL cholesterol	−0.04 [31]	0.08 [111]
Triacylglycerol	0.43[2] [31]	0.20[2] [111]
HDL cholesterol	−0.15 [31]	−0.16 [111]
8–9 y of age		
Systolic blood pressure	0.70[3] [31]	0.54[3] [111]
Diastolic blood pressure	0.58[3] [31]	0.37[3] [111]
Glucose	−0.05 [31]	0.17 [108]
Insulin	0.59[3] [31]	0.45[3] [85]
LDL cholesterol	0.19 [31]	0.23[2] [111]
Triacylglycerol	0.78[3] [31]	0.37[3] [111]
HDL cholesterol	−0.61[3] [31]	−0.22[2] [111]
11–12 y of age		
Systolic blood pressure	0.42[2] [30]	0.30[3] [109]
Diastolic blood pressure	0.43[2] [30]	0.18 [109]
Glucose	−0.04 [17]	0.04 [80]
Insulin	0.38[2] [29]	0.42[3] [101]
LDL cholesterol	0.01 [31]	0.11 [111]
Triacylglycerol	0.42[2] [31]	0.26[3] [110]
HDL cholesterol	−0.23[2] [31]	−0.18 [111]

[1] *n* values in brackets.
[2] $P \leq 0.05$.
[3] $P \leq 0.01$.

TABLE 3
Spearman's correlation coefficients (*r*) between BMI and other cardiovascular disease risk factors for boys by age group[1]

	Boys	
	Hypercholesterolemic	Nonhypercholesterolemic
5–6 y of age		
Systolic blood pressure	0.20 [27]	0.27[2] [104]
Diastolic blood pressure	0.13 [27]	0.27[2] [104]
Glucose	0.15 [23]	0.03 [82]
Insulin	0.26 [13]	0.04 [36]
LDL cholesterol	−0.12 [27]	−0.07 [104]
Triacylglycerol	−0.06 [27]	−0.14 [104]
HDL cholesterol	−0.001 [27]	0.11 [104]
8–9 y of age		
Systolic blood pressure	0.12 [26]	0.44[2] [104]
Diastolic blood pressure	0.10 [26]	0.32[2] [103]
Glucose	0.02 [27]	0.05 [103]
Insulin	0.15 [25]	0.19 [78]
LDL cholesterol	0.24 [27]	−0.03 [104]
Triacylglycerol	0.19 [27]	−0.04 [104]
HDL cholesterol	−0.21 [27]	−0.04 [104]
11–12 y of age		
Systolic blood pressure	0.17 [27]	0.35[2] [104]
Diastolic blood pressure	−0.30 [27]	0.05 [105]
Glucose	−0.21 [15]	0.10 [74]
Insulin	0.30 [24]	0.36[2] [83]
LDL cholesterol	0.11 [27]	−0.05 [104]
Triacylglycerol	0.29 [27]	0.12 [104]
HDL cholesterol	−0.07 [27]	−0.13 [104]

[1] *n* values in brackets.
[2] $P \leq 0.05$.

increased BMI expressed in the hypercholesterolemic girls in the current study was independent of race.

Studies that focus on the expression of other CVD risk factors, specifically in hyperlipidemic children, are limited. An association between age and blood lipid concentrations and an independent relation between relative weight and hyperlipidemia associated with familial combined hyperlipidemia was previously described in children with familial combined hyperlipidemia (42). Although data from the Bogalusa Heart Study are not specific for children with familial hyperlipidemia, these previous observations are consistent with the current findings, again suggesting that increased weight exacerbates hyperlipidemia in hyperlipidemic children, at least in girls. Also, the observation that adults with pure hypercholesterolemia did not have altered insulin sensitivity suggests that the expression of other CVD risk factors may differ among persons with different lipid disorders (43). This should be further evaluated in children and adults.

As opposed to these studies of hypercholesterolemic children, most published studies that evaluated the clustering of CVD risk factors in children focused on children from the general population without predefined risk factors (1–4, 7, 8, 16, 17, 23, 44–50) or on obese children (18–22, 26, 51). Webber et al (1) and Freedman et al (52) described a greater than expected prevalence of CVD risk factors, including increased cholesterol concentrations, blood pressure and weight-height index, in 5–17-y-old children but not in preschool children. Boulton and Johnston (16) confirmed this lack of clustering of risk factors in 4-y-old children. These results are consistent with the age-related associations we described in hypercholesterolemic children. The potential long-term effect of these risk factors at a young age is suggested by the fact that risk factors, such as high insulin concentrations, track from childhood into early adulthood, and higher insulin concentrations cluster with higher relative weights, higher blood pressure, and adverse changes in lipids and lipoproteins (8, 16).

Despite the consistency of our findings, it is not clear how hypercholesterolemia is linked to high adiposity. It seems more likely that hypercholesterolemia acts as a marker of altered metabolism, which results in excessive adiposity. This is supported by the higher triacylglycerol concentrations in the hypercholesterolemic children at baseline. The hypercholesterolemic children described here at baseline may have been a pediatric variant of metabolically obese, normal-weight adults, ie, adults with normal body weight but who express a cluster of obesity-related characteristics (53, 54). However, because these hypercholesterolemic girls go on to express an increasing BMI, a more appropriate descriptive phrase for these children may be "metabolically obese, preobese." Ultimately, the increased relative weight these girls displayed was associated with increased blood pressure and insulin concentrations. In addition, the association between BMI and lipid concentrations suggests that obesity further exacerbates dyslipidemia. This is consistent with the hypothesis that hyperinsulinemia (associated with increased adiposity) also induces or exacerbates dyslipidemia (14). Because the study of older children and adults may be complicated by secondary changes or by

adaptations that occur with age or time, it is clear that future studies should evaluate the longitudinal expression of and interaction between high adiposity, dyslipidemia, and hyperinsulinemia in young children.

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REFERENCES

1. Webber LS, Voors AW, Srinivasan SR, Frerichs RR, Berenson GS. Occurrence in children of multiple risk factors for coronary artery disease: The Bogalusa Heart Study. Prev Med 1979;8:407–18.
2. Wilmore JH, McNamara JJ. Prevalence of coronary heart disease risk factors in boys, 8 to 12 years of age. J Pediatr 1974;84:527–33.
3. Lauer RM, Connor WE, Leaverton PE, Reiter MA, Clarke WR. Coronary heart disease risk factors in school children: the Muscatine study. J Pediatr 1975:697–706.
4. Raitakari OT, Porkka KVK, Ronnemaa T, et al. The role of insulin in clustering of serum lipids and blood pressure in children and adolescents. The Cardiovascular Risk in Young Finns Study. Diabetologia 1995;38:1042–50.
5. Guo S, Salisbury S, Roche AF, Chumlea WC, Siervogel RM. Cardiovascular disease risk factors and body composition: a review. Nutr Res 1994;11:1721–77.
6. Chen W, Srinivasan SR, Elkasabany A, Berenson GS. Cardiovascular risk factors clustering features of insulin resistance syndrome (syndrome X) in a biracial (black-white) population of children, adolescents, and young adults: the Bogalusa Heart Study. Am J Epidemiol 1999;150:667–74.
7. Burke GL, Webber LS, Srinivasan SR, Radhakrishnamurthy B, Freedman DS, Berenson GS. Fasting plasma glucose and insulin levels and their relationship to cardiovascular risk factors in children: Bogalusa Heart Study. Metabolism 1986;35:441–6.
8. Jiang X, Srinivasan SR, Webber LS, Wattigney WA, Berenson GS. Association of fasting insulin level with serum lipid and lipoprotein levels in children, adolescents, and young adults: the Bogalusa Heart Study. Arch Intern Med 1995;155:190–6.
9. Walker M. Obesity, insulin resistance, and its link to non-insulin-dependent diabetes mellitus. Metabolism 1995;44:18–20.
10. Kissebah AH, Peiris AN. Biology of regional body fat distribution: relationship to non-insulin-dependent diabetes mellitus. Diabetes Metab Rev 1989;15:83–109.
11. Howard BV, Mayer-Davis EJ, Goff D, et al. Relationships between insulin resistance and lipoproteins in nondiabetic African Americans, Hispanics, and non-Hispanic Whites: the Insulin Resistance Atherosclerosis Study. Metabolism 1998;47:1174–9.
12. Blaak EE, Saris WHM, Wolffenbuttel BHR. Substrate utilization and thermogenic responses to β-andrenergic stimulation in obese subjects with NIDDM. Int J Obes Relat Metab Disord 1999;23:411–8.
13. Okosun IS, Cooper RS, Prewitt E, Rotimi CN. The relation of central adiposity to components of the insulin resistance syndrome in a biracial US population sample. Ethnic Dis 1999;9:218–29.
14. Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriacyglycerolemia: historical perspective and review of biological mechanisms. Am J Clin Nutr 2000;71:412–33.
15. Boulton TJC, Johnston O. A coronary risk-factor profile of 4 year olds. II. Inter-relationships, clustering, and tracking of blood pressure, serum lipoproteins, and skinfold thickness. Aust Paediatr J 1978;14:278–82.
16. Smoak CG, Burke GL, Webber LS, Harsha DW, Srinivasan SR, Berenson GS. Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults. The Bogalusa Heart Study. Am J Epidemiol 1987;125:364–72.
17. Jiang X, Srinivasan SR, Urbina E, Berenson GS. Hyperdynamic circulation and cardiovascular risk in children. The Bogalusa Heart Study. Circulation 1995;91:1101–6.
18. Brambilla P, Manzoni P, Sironi S, et al. Peripheral and abdominal adiposity in childhood obesity. Int J Obes Relat Metab Disord 1994;18:795–800.
19. Caprio S, Hyman LD, McCarthy S, Lange R, Bronson M, Tamborlane WV. Fat distribution and cardiovascular risk factors in obese adolescent girls: importance of the intraabdominal fat depot. Am J Clin Nutr 1996;64:12–7.
20. Monti LD, Brambilla P, Stefani I, et al. Insulin regulation of glucose turnover and lipid levels in obese children with fasting normoinsulinaemia. Diabetologia 1995;38:739–47.
21. Waliu Islam AHM, Yamashita S, Kotani K, et al. Fasting plasma insulin level is an important risk factor for the development of complications in Japanese obese children—results from a cross-sectional and a longitudinal study. Metabolism 1995;4:478–85.
22. Agostoni C, Riva E, Bellu R, Vincenzo SS, Grazia BM, Giovanni M. Relationships between the fatty acid status and insulinemic indexes in obese children. Prostaglandins Leukot Essent Fatty Acids 1994;51:317–21.
23. Frerichs RR, Webber LS, Srinivasan SR, Berenson GS. Relation of serum lipids and lipoproteins to obesity and sexual maturity in white and black children. Am J Epidemiol 1978;108:486–96.
24. Shear CL, Freedman DS, Burke GL, Harsha DW, Berenson GS. Body fat patterning and blood pressure in children and young adults. The Bogalusa Heart Study. Hypertension 1987;9:236–44.
25. Kikuchi DA, Srinivasan SR, Harsha DW, Webber LS, Sellers TA, Berenson GS. Relation of serum lipoprotein lipids and apolipoproteins to obesity in children: the Bogalusa Heart Study. Prev Med 1992;21:177–90.
26. Zwiauer KFM, Pakosta R, Mueller T, Widhalm K. Cardiovascular risk factors in obese children in relation to weight and body fat distribution. J Am Coll Nutr 1992;11:41S–50S.
27. Ronnemaa T, Knip M, Lautala P, et al. Serum insulin and other cardiovascular risk indicators in children, adolescents and young adults. Ann Med 1991;23:67–72.
28. Le Stunff C, Bougneres P-F. Time course of increased lipid and decreased glucose oxidation during early phase of childhood obesity. Diabetes 1993;42:1010–6.
29. Tershakovec AM, Jawad AF, Stallings VA, Cortner JA, Zemel BS, Shannon BM. Age-related changes in cardiovascular disease risk factors of hypercholesterolemic children. J Pediatr 1998;132:414–20.
30. Berenson GS, McMahan CA, Voors AW, et al. Cardiovascular risk factors in children—the early natural history of atherosclerosis and essential hypertension. New York: Oxford University Press, 1980:1–450.
31. Lipid Research Clinics Program. Manual of laboratory operations. I: Lipid and lipoprotein analysis. Washington, DC: US Government Printing Office, 1974. [DHEW publication (NIH)75-828.]
32. Allain CC, Poon LS, Chan CSG, Richmond W, Wu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470–5.
33. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 1973:19:476–82.
34. Srinivasan SR, Berenson GS. Serum lipoprotein in children and methods for study. In: Lewis LA, ed. CRC handbook of electrophoresis. III: Lipoprotein methodology and human studies. Boca Raton, FL: CRC Press, Inc, 1983:185–204.
35. SAS Institute, Inc. SAS release 6.12. Cary, NC: SAS Institute, Inc, 1989–1996.
36. SPSS, Inc. SPSS release 9.0. Chicago: SPSS, Inc, 1980–1999.
37. Centers for Disease Control, National Center for Health Statistics. Individual growth charts. Internet: http://www.cdc.gov/growthcharts (accessed 4 August 2001).
38. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128:608–15.
39. Svec F, Nastasi K, Hilson C, Bao W, Srinivasan SR, Berenson GS.

Black-white contrasts in insulin levels during pubertal development. The Bogalusa Heart Study. Diabetes 1992;41:313–7.
40. Bao W, Srinivasan SR, Wattigney WA, Bao W, Berenson GS. Usefulness of childhood low-density lipoprotein cholesterol level in predicting adult dyslipidemia and other cardiovascular risks. Arch Intern Med 1996;156:1315–20.
41. Morrison JA, Barton B, Biro FM, Sprecher DL, Falkner F, Obarzanek E. Sexual maturation and obesity in 9- and 10-year-old black and white girls: the National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 1994;124:889–95.
42. Shamir R, Tershakovec AM, Gallagher PR, Liacouras CA, Hayman LA, Cortner JA. The influence of age and relative weight on the presentation of familial combined hyperlipidemia in childhood. Atherosclerosis 1996;121:85–91.
43. Karhapaa P, Voutilainen E, Kovanen PT, Laakso M. Insulin resistance in familial and nonfamilial hypercholesterolemia. Arterioscler Thromb 1993;13:41–7.
44. Arslanian S, Suprasongsin C. Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents. J Pediatr 1996;129:440–3.
45. Daniels SR, Obarzanek E, Barton BA, Kimm SYS, Similo SL, Morrison JA. Sexual maturation and racial differences in blood pressure in girls: the National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 1996;129:208–13.
46. Craig SB, Bandini LG, Lichtenstein AH, Schaefer EJ, Dietz WH. The impact of physical activity on lipids, lipoproteins, and blood pressure in preadolescent girls. Pediatrics 1996;98:389–95.
47. Travers SH, Jeffers BW, Bloch CA, Hill JO, Eckel RH. Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J Clin Endocrinol Metab 1995; 80:172–8.
48. Jiang X, Srinivasan SR, Radhakrishnamurthy B, Dalferes ER Jr, Berenson GS. Racial (black-white) differences in insulin secretion and clearance in adolescents: the Bogalusa Heart Study. Pediatrics 1996;97:357–60.
49. Bao W, Srinivasan SR, Berenson GS. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults: the Bogalusa Heart Study. Circulation 1996; 93:54–9.
50. Braun B, Zimmermann MB, Kretchmer N, Sparago RM, Smith RM, Gracey M. Risk factors for diabetes and cardiovascular disease in young Australian aborigines: a 5-year follow-up study. Diabetes Care 1996;19:472–9.
51. Hoffman RP, Stumbo PJE, Janz KF, Nielsen DH. Altered insulin resistance is associated with increased dietary weight loss in obese children. Horm Res 1995;44:17–22.
52. Freedman DS, William WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics 1999;103: 1175–82.
53. Dvorak RV, DeNino WF, Ades PA, Poehlman ET. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal weight young women. Diabetes 1999;48:2210–4.
54. Ruderman NB, Schneider SH, Berchtold P. The "metabolically obese," normal weight individual. Am J Clin Nutr 1981;34:1617–21.