Insulin Resistance

Link to the components of the metabolic syndrome and biomarkers of endothelial dysfunction in youth

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OBJECTIVE — We examined the relationship of in vivo insulin sensitivity to the components of the metabolic syndrome and biomarkers of endothelial dysfunction in youth.

RESEARCH DESIGN AND METHODS — Subjects included 216 youths (8–19 years of age) who participated in a 3-h hyperinsulinemic-euglycemic clamp.

RESULTS — Independent of race, the frequencies of central obesity, high triglycerides, low HDL, high blood pressure, impaired fasting glucose, and impaired glucose tolerance were significantly higher ($P < 0.05$) in the lowest versus highest quartile of insulin sensitivity. BMI, abdominal adiposity, systolic blood pressure, and triglycerides increased and adiponectin and HDL decreased significantly (P for trend for all <0.05), with decreasing insulin sensitivity in both races. After controlling for BMI, insulin resistance remained associated ($P < 0.05$) with visceral adipose tissue in both races (P for trend = 0.01 in blacks and 0.08 in whites). In whites but not blacks, lower insulin sensitivity was associated ($P < 0.05$) with higher intercellular adhesion molecule-1 (ICAM-1) and E-selectin levels; however, these relationships did not remain significant ($P > 0.05$) once visceral adipose tissue was controlled for.

CONCLUSIONS — The prevalence of the individual components of metabolic syndrome increases with decreasing insulin sensitivity in black and white youth. In whites but not blacks, insulin resistance is associated with increased circulating endothelial biomarkers. It remains to be determined if lower abdominal adiposity and triglycerides in blacks underlies the racial differences in risk translation.

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The escalating epidemic of childhood obesity is of great public health concern because of the obesity-related comorbid conditions in youth, such as high blood pressure (BP) (1,2), insulin resistance (3,4), and type 2 diabetes (5). As in adults, the prevalence of the metabolic syndrome, a cluster of risk factors for cardiovascular disease (CVD) and type 2 diabetes (6), is high in overweight youth (7–9). Despite several definitions for metabolic syndrome in adults, there are currently no accepted criteria in pediatrics. Previous studies, however, have used variations of the adult criteria to report a wide range of metabolic syndrome prevalence rates in youth (7–10).

Although insulin resistance is proposed to be the underlying mechanism linking the various components of the metabolic syndrome (6), studies exploring the relationship between directly measured insulin resistance and the components of metabolic syndrome are lacking in pediatrics. Therefore, we examined the individual components of the metabolic syndrome based on quartiles of in vivo insulin sensitivity in children and adolescents.

Elevated CVD risk factors in childhood are associated with risk of atherosclerotic disease in adulthood (11,12). During the early stages of atherosclerotic CVD, biomarkers of endothelial dysfunction including intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin are increased in response to inflammatory cytokines and play an important role in the formation of atherosclerotic plaque (13). Although the relationship between circulating adhesion molecules and insulin resistance is well documented in adults (14–16), it is unclear if this holds true in youth. Thus, we examined the relationship between insulin sensitivity and the biomarkers of endothelial dysfunction.

RESEARCH DESIGN AND METHODS

— Subjects consisted of 99 black and 117 white youth (8–19 years) who underwent assessment of in vivo insulin sensitivity at Children's Hospital of Pittsburgh. Data from some of these subjects have been reported previously (3,17–20). Exclusion criteria included diagnosed diabetes or any chronic illness and the use of medications that influence glucose and lipid metabolism and BP. All study participants were recruited through newspaper advertisements in the greater Pittsburgh area, flyers posted in the city public transportation, and posters placed on campus. The investigation was approved by the institutional review board, parental informed consent and child assent were obtained from all participants, and studies were performed in the General Clinical Research Center of Children's Hospital of Pittsburgh. All participants underwent a physical examination and routine hematological and biochemical tests. Pubertal development was assessed by Tanner criteria. The overweight subjects (BMI ≥95th percentile) (21) underwent an oral glucose tolerance test before participation to screen for normal glucose tolerance. Among 105 over-

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Abbreviations: BP, blood pressure; CVD, cardiovascular disease; ICAM-1, intercellular adhesion molecule-1; IGT, impaired glucose tolerance; IL, interleukin; ROC, receiver-operating characteristic; VAT, visceral adipose tissue; VCAM-1, vascular adhesion molecule-1.

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

Table 1—*Subject characteristics*

	Blacks	Whites	*P*
n	99	117	
Sex (M/F)	39/60	52/65	
Prepubertal, Tanner I	20 (20.2)	21 (17.9)	NS
Pubertal, Tanner II–V	79 (79.8)	96 (82.1)	NS
Age (years)	12.3 ± 0.2	12.9 ± 0.2	NS
BMI (kg/m^2)	26.9 ± 0.9	26.5 ± 0.9	NS
BMI *z* score	1.4 ± 0.1	1.2 ± 0.1	NS
Waist circumference (cm)*	80.8 ± 2.6	82.5 ± 2.3	NS
VAT (cm^2)†	39.5 ± 3.5	51.6 ± 4.1	0.029
Subcutaneous adipose tissue (cm^2)†	281.5 ± 23.9	296.6 ± 22.8	NS
Triglycerides (mg/dl)	84.6 ± 4.6	120.0 ± 6.3	<0.001
HDL (mg/dl)	46.5 ± 1.2	44.1 ± 0.9	NS
LDL (mg/dl)	94.1 ± 2.9	97.3 ± 2.6	NS
VLDL (mg/dl)	16.9 ± 0.9	23.9 ± 1.3	<0.001
Morning systolic BP (mmHg)	108.8 ± 1.1	108.3 ± 1.1	NS
Morning diastolic BP (mmHg)	63.4 ± 0.8	60.6 ± 0.7	0.008
Fasting glucose (mg/dl)	95.9 ± 0.7	95.9 ± 0.5	NS
Fasting insulin (μU/ml)	31.5 ± 2.3	30.1 ± 2.1	NS
Insulin sensitivity (mg · kg^{-1} · min^{-1} per μU/ml)	6.5 ± 0.5	7.2 ± 0.6	NS
Adiponectin (μg/ml)‡	9.9 ± 0.6	10.8 ± 0.6	NS
IL-6 (pg/ml)§	1.9 ± 0.2	1.5 ± 0.1	NS
VCAM-1 (ng/ml)‖	422.1 ± 16.1	519.7 ± 14.8	<0.001
ICAM-1 (ng/ml)#	270.7 ± 10.0	309.8 ± 8.0	0.002
E-selectin (ng/ml)‖	64.9 ± 2.6	62.2 ± 2.9	NS
Polycystic ovarian syndrome	12 (12.1)	14 (12.0)	NS
Prevalence**			
Large waist circumference*	20 (33.9)	35 (37.2)	NS
High triglycerides	19 (19.2)	49 (41.9)	<0.001
Low HDL	34 (34.3)	41 (35.0)	NS
High BP	17 (17.2)	13 (11.1)	NS
IFG and IGT	27 (27.3)	35 (29.9)	NS

Data are *n*, *n* (%), or means ± SE. *n = 59 in blacks and n = 94 in whites. †n = 95 in blacks and n = 112 in whites. ‡n = 97 in blacks. §n = 90 in blacks and n = 110 in whites. ‖n = 98 in blacks. #n = 92 in blacks. **Based on the modified National Cholesterol Education Program/Adult Treatment Panel III criteria, large circumference (≥90th percentile for age, sex, and race), high triglycerides (≥110 mg/dl), low HDL (≤40 mg/dl), high BP (systolic or diastolic BP ≥90th percentile for age, sex, and height) (27), and impaired fasting glucose (IFG, ≥100 mg/dl) (28) or IGT (22).

weight subjects (50 blacks and 55 whites), 24 subjects [10 blacks (7 with polycystic ovarian syndrome) and 14 whites (10 with polycystic ovarian syndrome)] had impaired glucose tolerance (IGT) (22). Among 125 girls, 26 subjects had polycystic ovarian syndrome referred to the endocrine service for evaluation of irregular menses, hirsutism, and acne, as reported previously (23–25).

Abdominal adiposity

Waist circumference was obtained in 153 subjects at the midpoint between the lowest rib and the iliac crest. A single transverse image of the abdomen (L4–L5) was obtained using computed tomography in 207 subjects, as shown by us previously (26).

Hyperinsulinemic-euglycemic clamp

All subjects were admitted to the General Clinical Research Center on the afternoon before the day of the clamp experiment, after assuring that they had not had any intercurrent illnesses for the preceding 3–4 weeks. The clamp was performed after a 10- to 12-h overnight fast, where fasting blood was obtained for lipid profile, adiponectin, interleukin (IL)-6, and adhesion molecules. Briefly, the 3-h hyperinsulinemic-euglycemic clamp was performed with plasma glucoses clamped at 5.6 mmol/l with a variable rate infusion of 20% dextrose based on arterialized plasma glucose determinations every 5 min, as previously described (19,25). The insulin-stimulated glucose disposal rate was calculated using the average exogenous glucose infusion rate during the final 30 min of the clamp. Insulin sensitivity (mg · kg^{-1} · min^{-1} per μU/ml × 100) was calculated by dividing the insulin-stimulated glucose disposal rate by the steady-state insulin levels during the last 30 min of the clamp as described previously (19).

Definition of the individual components of the metabolic syndrome

We used cutoffs using the modified National Cholesterol Education Program/Adult Treatment Panel III criteria similar to those published previously (7,10): high triglycerides (≥110 mg/dl), low HDL (≤40 mg/dl), high BP (systolic or diastolic BP ≥90th for age, sex, and height) (27), impaired fasting glucose (≥100 mg/dl) (28) or IGT (22), and large waist (≥90th for age, sex, and race) (29).

Biochemical measurements

The measurements of plasma glucose, insulin, lipids, and adiponectin are described by us previously (18). IL-6 (highly sensitive solid-phase assay kits), ICAM-1, VCAM-1, and E-selectin were quantified using commercially available double-sandwich enzyme-linked immunoassays (R&D Systems, Minneapolis, MN). The intra- and interassay coefficients of variation were: 6.7 and 8.6% for IL-6, 6.0 and 9.4% for ICAM-1, 4.5 and 9.0% for VCAM-1, and 6.1 and 9.0% for E-selectin, respectively.

Statistical analysis

Statistical procedures were performed using SPSS 14.0 (SPSS, Chicago, IL). Independent *t* tests were used to examine subject characteristics. ANCOVA, adjusted for age, sex, and Tanner stage (prepubertal and pubertal), was used to compare metabolic variables between the quartiles of insulin sensitivity groups within each race. Frequencies of the individual components of metabolic syndrome were compared using the χ^2 tests between the quartiles of insulin sensitivity groups. Receiver-operating characteristic (ROC) curves were used to obtain the area under the curve, an indicator of the ability of metabolic syndrome components to discriminate the subjects with insulin resistance versus without insulin resistance. Multiple regression analyses were used to examine the independent contribution of insulin sensitivity and visceral adipose tissue (VAT) to the metabolic markers.

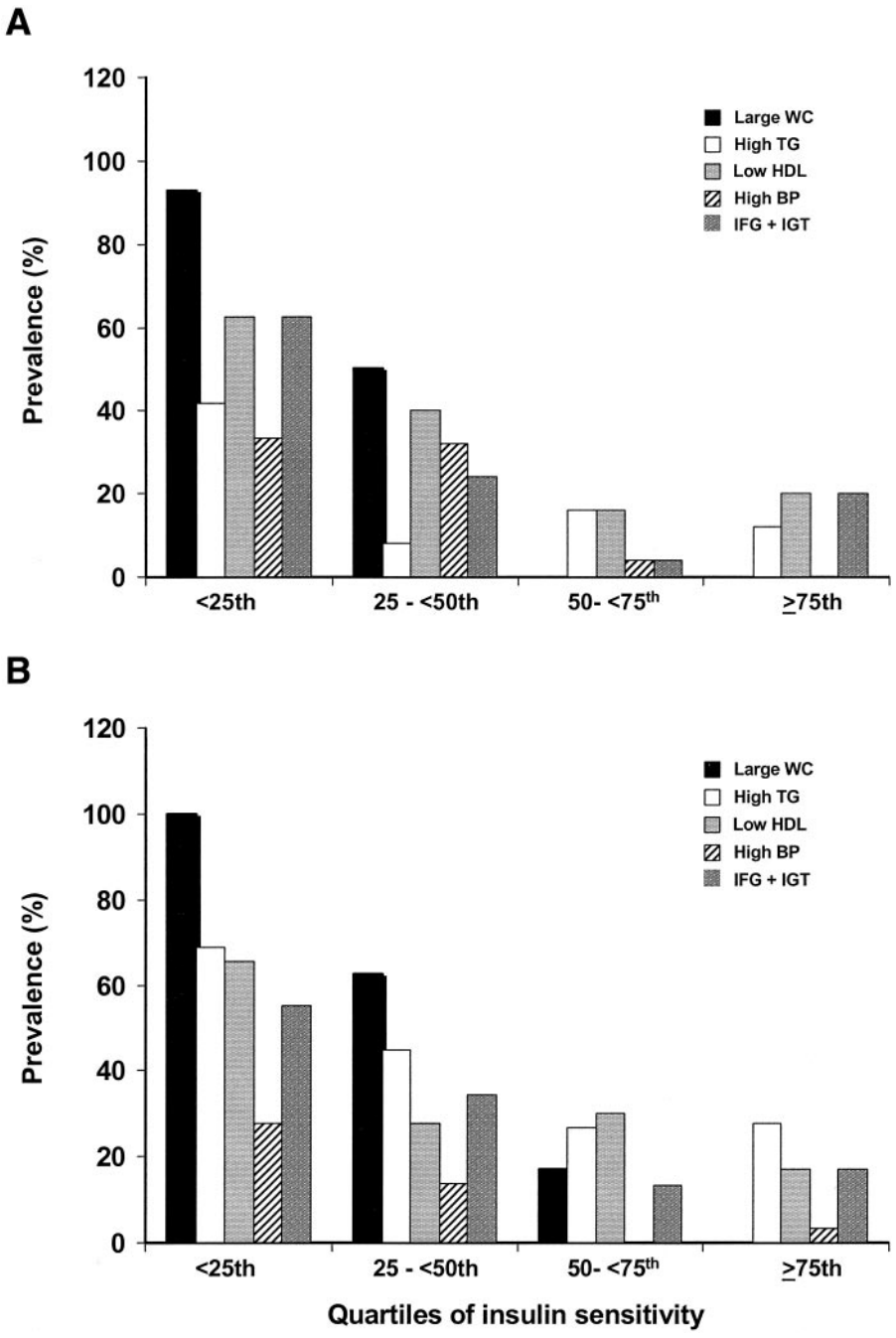

Figure 1—*The prevalence of the individual components of metabolic syndrome by quartiles of insulin sensitivity in black* (A) *and white* (B) *youth. Impaired fasting glucose (IFG) (≥100 mg/dl) (28) plus IGT (22) is shown. Mean insulin sensitivity in the lowest quartile: blacks, 1.2 ± 0.1 mg · kg^{-1} · min^{-1} per μU/ml; whites, 1.3 ± 0.1 mg · kg^{-1} · min^{-1} per μU/ml. Mean insulin sensitivity in the highest quartile: blacks, 13.5 ± 0.5 mg · kg^{-1} · min^{-1} per μU/ml; whites, 15.8 ± 0.8 mg · kg^{-1} · min^{-1} per μU/ml. TG, triglycerides; WC, waist circumference.*

RESULTS — The subject characteristics are shown in Table 1. Independent of race, the frequencies of central obesity, high triglycerides, low HDL, high BP, impaired fasting glucose, and IGT were higher ($P <$ 0.05) in the lowest versus highest quartile of insulin sensitivity (Fig. 1). In the lowest quartile of the insulin sensitivity group, central obesity had the highest prevalence (92.9%) among all components of the metabolic syndrome in blacks followed by low HDL (62.5%) and impaired fasting glucose plus IGT (62.5%). In whites, central obesity (100%) was the most common feature followed by high triglycerides (69%) and low HDL (65.5%).

Figures 2 and 3 indicate the individual components of metabolic syndrome, circulating adhesion molecules, adiponectin and IL-6 levels (after adjusting for age, sex, and Tanner stage) stratified by quartiles of insulin sensitivity. BMI, systolic BP, triglycerides, and abdominal adiposity (waist circumference and VAT) decreased (P for trend <0.01) and HDL increased with increasing insulin sensitivity in both races (Fig. 2). After further adjustment for BMI, VAT decreased with increasing insulin sensitivity in both races (P for trend $= 0.01$ in blacks and 0.08 in whites). In the lowest quartile of insulin sensitivity group, VAT ($P = 0.036$), waist circumference ($P = 0.027$), and triglycerides ($P = 0.088$) were higher in whites versus blacks.

As shown in Fig. 3, in whites but not blacks, ICAM-1, E-selectin, and IL-6 levels significantly decreased (P for trend <0.01) with increasing insulin sensitivity; however, these relationships did not remain significant (P for trend >0.1 for all) after controlling for BMI. Further, adiponectin levels increased significantly (P for trend <0.01) in a stepwise manner from the lowest to the highest quartiles of insulin sensitivity in both races, and these observations remained significant (P for trend <0.01 for both races) after further adjustment for BMI.

Figure 4 indicates the ROC curves of the metabolic syndrome components as markers of insulin resistance. Independent of race, the greatest area under the ROC curves as markers of insulin resistance were BMI (blacks: 0.972, whites: 0.928) and waist circumference (blacks: 0.950, whites: 0.943).

In multiple regression analyses with insulin sensitivity as the dependent variable and BMI, waist circumference, triglycerides, BP, or HDL as the independent variables with age, race, and sex, the R^2 for BMI and waist circumference were 0.75 and waist circumference 0.74 (data not shown). In the same analyses, the R^2 for triglycerides, BP, and HDL were 0.33, 0.41, and 0.31, respectively (data not shown).

Independent contribution of insulin sensitivity and VAT to the metabolic syndrome components and adhesion molecules

In blacks, insulin sensitivity was independently related to triglycerides (partial $r = -0.29$, $P < 0.05$) and HDL (partial $r = 0.29$, $P < 0.05$), while in whites, VAT was independently associated with these

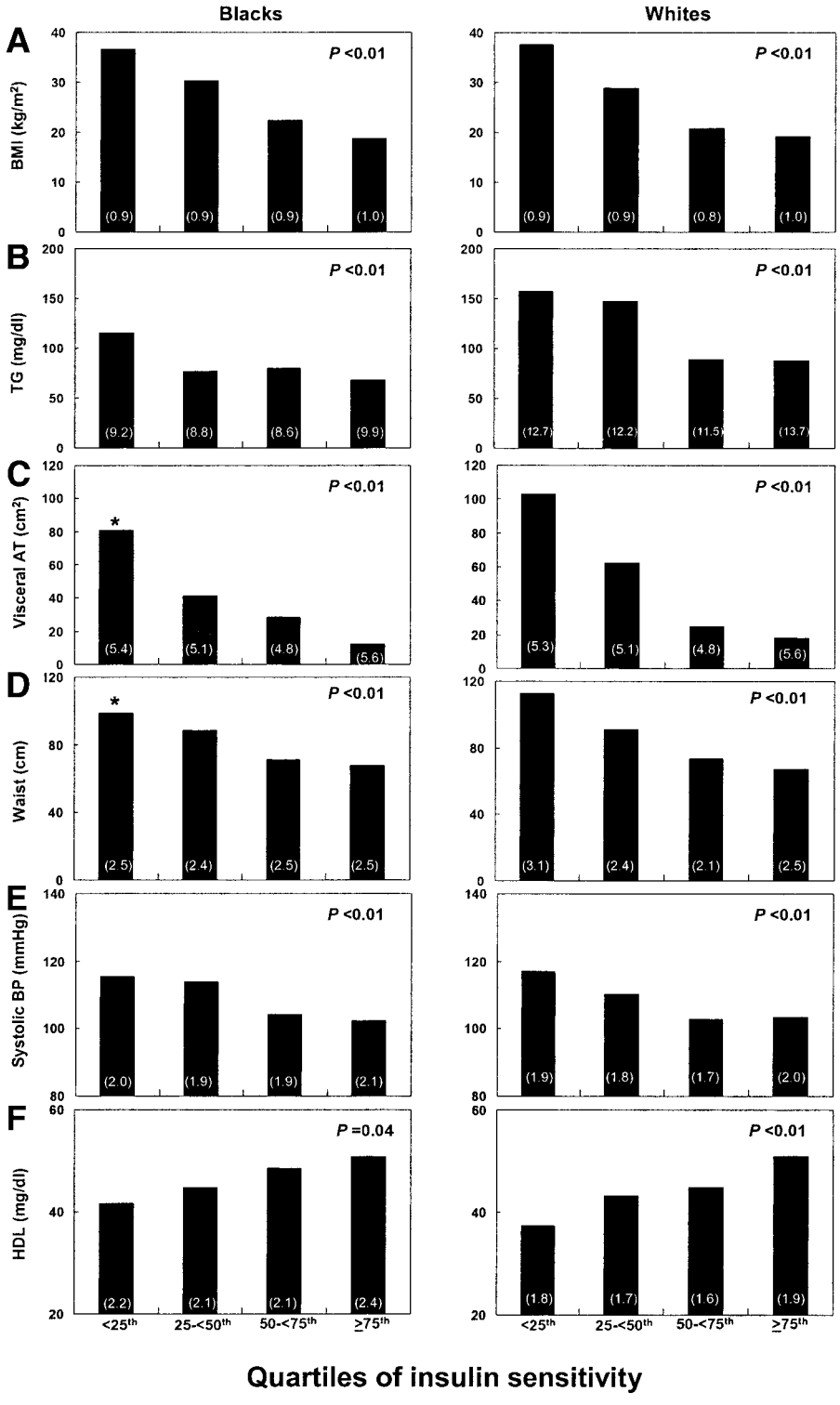

Figure 2—*Individual components of metabolic syndrome and abdominal adiposity in black and white youth according to quartiles of insulin sensitivity. *Significantly different (*$P < 0.05$*) between blacks versus whites in the lowest quartile of insulin sensitivity group. Data are shown as estimated marginal means after adjusting for age, sex, and Tanner stage. SE (±) is shown in parentheses in the bars. AT, adipose tissue; TG, triglycerides.*

markers (triglycerides: partial $r = 0.23$, $P < 0.05$, HDL: partial $r = -0.22$, $P < 0.05$) after accounting for age, sex, and Tanner stage. In both races, VAT was associated ($P < 0.05$) with systolic BP independent of insulin sensitivity (partial $r = 0.26$ and $r = 0.25$ in blacks and whites, respectively). In whites, VAT was associated with ICAM-1 (partial $r = 0.17$, $P = 0.08$) and E-selectin (partial $r = 0.25$, $P < 0.01$) independent of insulin sensitivity.

CONCLUSIONS— Our findings demonstrate the following: *1*) the prevalence of the individual components of metabolic syndrome increases with decreasing in vivo insulin sensitivity; *2*) adiponectin segregates with the degree of insulin sensitivity; *3*) in whites, insulin resistance is significantly associated with higher IL-6 and biomarkers of endothelial dysfunction, ICAM-1, and E-selectin; *4*) significant racial differences exist in the level of the individual components of metabolic syndrome, mainly abdominal adiposity and triglycerides; and, last but not least, *5*) although obesity plays a major role in the clustering of metabolic syndrome, insulin resistance is also associated with VAT and adiponectin after controlling for BMI.

Similar to findings in adults, our study in youth demonstrates that all of the components of metabolic syndrome substantially increase with the degree of insulin resistance independent of race. Given that most of our subjects in the most insulin-resistant group met the abdominal obesity criteria and that the greatest area under the ROC curves as markers of insulin resistance were waist circumference values, it is reasonable to assume that the relationships between insulin resistance and metabolic syndrome could be modulated by abdominal adiposity. Indeed, in our multiple regression analyses, VAT predicts triglycerides and HDL in whites and systolic BP in both races independent of insulin sensitivity. Given that anthropometric measures of BMI or waist circumference provide the highest variance in insulin sensitivity in our study, such measures constitute important clinical markers of metabolic risk in youth, and in the absence of a pediatric definition of metabolic syndrome, a measure of abdominal obesity (waist circumference) should be considered as an important component of the pediatric metabolic syndrome definition.

Our findings of high levels of adhesion molecules in white versus black youth are consistent with findings in adults (30). Our study suggests that racial differences in circulating adhesion molecules are already present during childhood. However, unlike the previous report (30) demonstrating significant sex differences in soluble adhesion molecules in a large sample of middle-aged men and

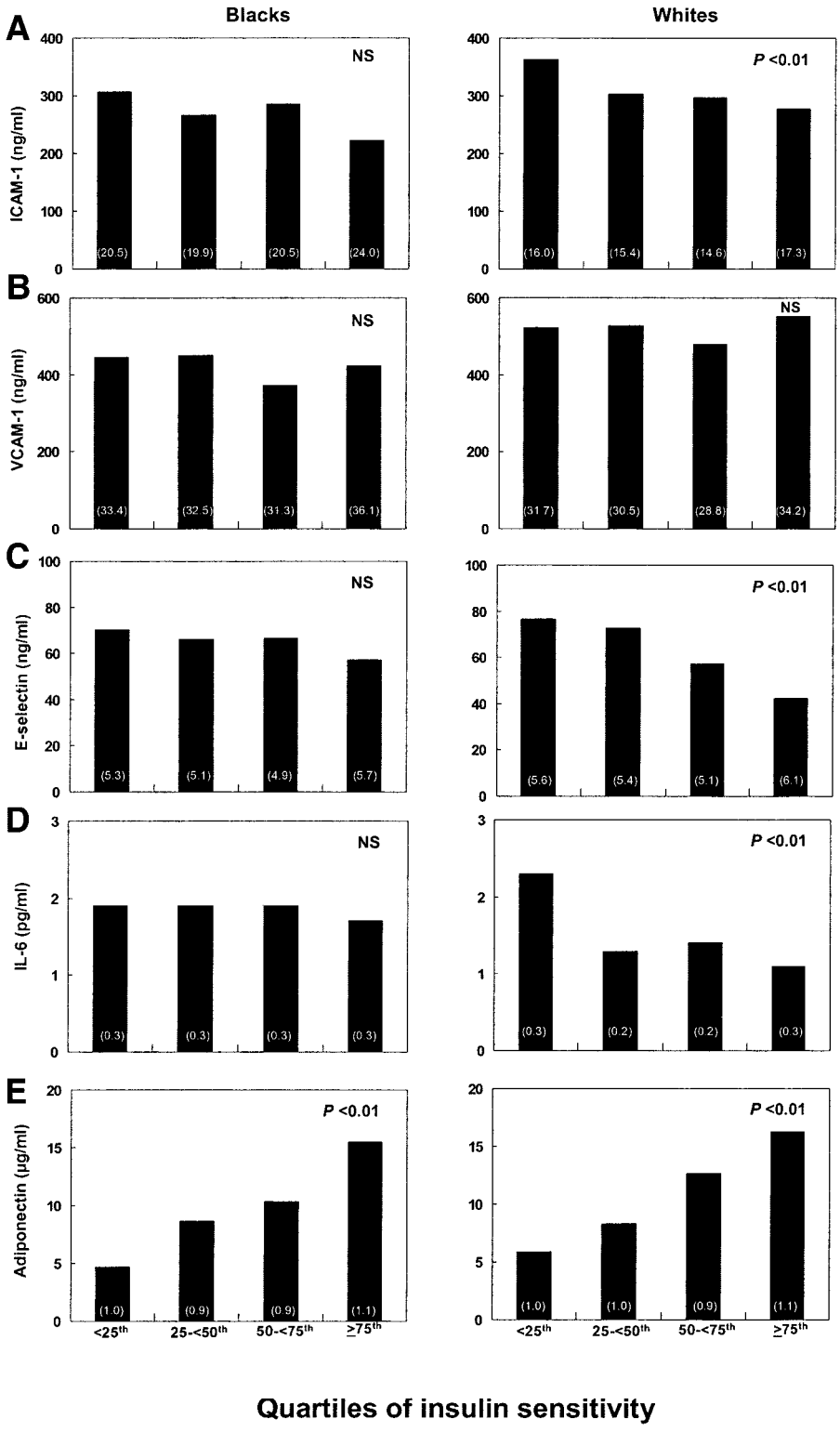

Figure 3—*Circulating biomarkers of endothelial dysfunction, adiponectin, and IL-6 in black and white youth according to quartiles of insulin sensitivity. *Significantly different* ($P < 0.05$) *between blacks versus whites in the lowest quartile of insulin sensitivity group. Data are shown estimated marginal means after adjusting for age, sex, and Tanner stage. SE (±) is shown in parentheses in the bars.*

women (aged 40–59 years), we observed a sex difference in VCAM-1 levels in blacks only (boys: 378.9 ± 20.0 vs. girls: 450.7 ± 22.7, $P = 0.028$). In addition, the observation that in whites the relationship between insulin sensitivity, ICAM-1, and E-selectin levels disappears after controlling for VAT is consistent with Targher et al. (31), who reported a similar finding in Caucasian adults with type 2 diabetes. These findings suggest that excess adiposity may contribute to increased circulating levels of adhesion molecules.

Our findings of a significant relationship between directly measured insulin resistance and endothelial markers in whites extend the previous observations in obese children (32,33), wherein insulin resistance was evaluated by homeostasis model assessment of insulin resistance. However, the underlying cause for the race-related differences in the levels of some of the adhesion molecules and their relationship or lack of, in the case of blacks, with insulin sensitivity remains to be determined. If visceral adiposity plays a role in circulating adhesion molecules, it would be tempting to theorize that the race-related differences may stem from the fact that blacks have significantly lower VAT than whites, a finding consistent with studies in adults (34,35). In parallel with lower VAT, blacks have lower triglycerides than whites similar to previous reports in youths (36) and adults (37). By contrast, blacks tend to have a greater prevalence of hypertension than whites (38). These observations raise the concerns about the validity of the current metabolic syndrome definitions and the theoretical question of whether or not it is reasonable to accept the same cutoff criteria of metabolic syndrome for triglycerides and BP in African-Americans and Caucasians.

Although the mechanisms by which VAT is associated with coronary artery disease risk are uncertain, VAT is now recognized as an endocrine tissue that produces inflammatory markers including tumor necrosis factor-α, plasma activator inhibitor-1, and IL-6, all of which are thought to play an important role in the development of atherosclerotic CVD (16). In this study, we observed that, in whites, VAT is strongly associated with circulating IL-6, ICAM-1, and E-selectin levels. It is plausible that higher VAT in whites may explain the greater atherogenic risk profile than in blacks, which is consistent with our previous finding (36). Future studies are needed to examine if the thresholds for the future development of CVD or type 2 diabetes are comparable between the two racial groups.

We observed that plasma adiponectin level increased significantly with increasing

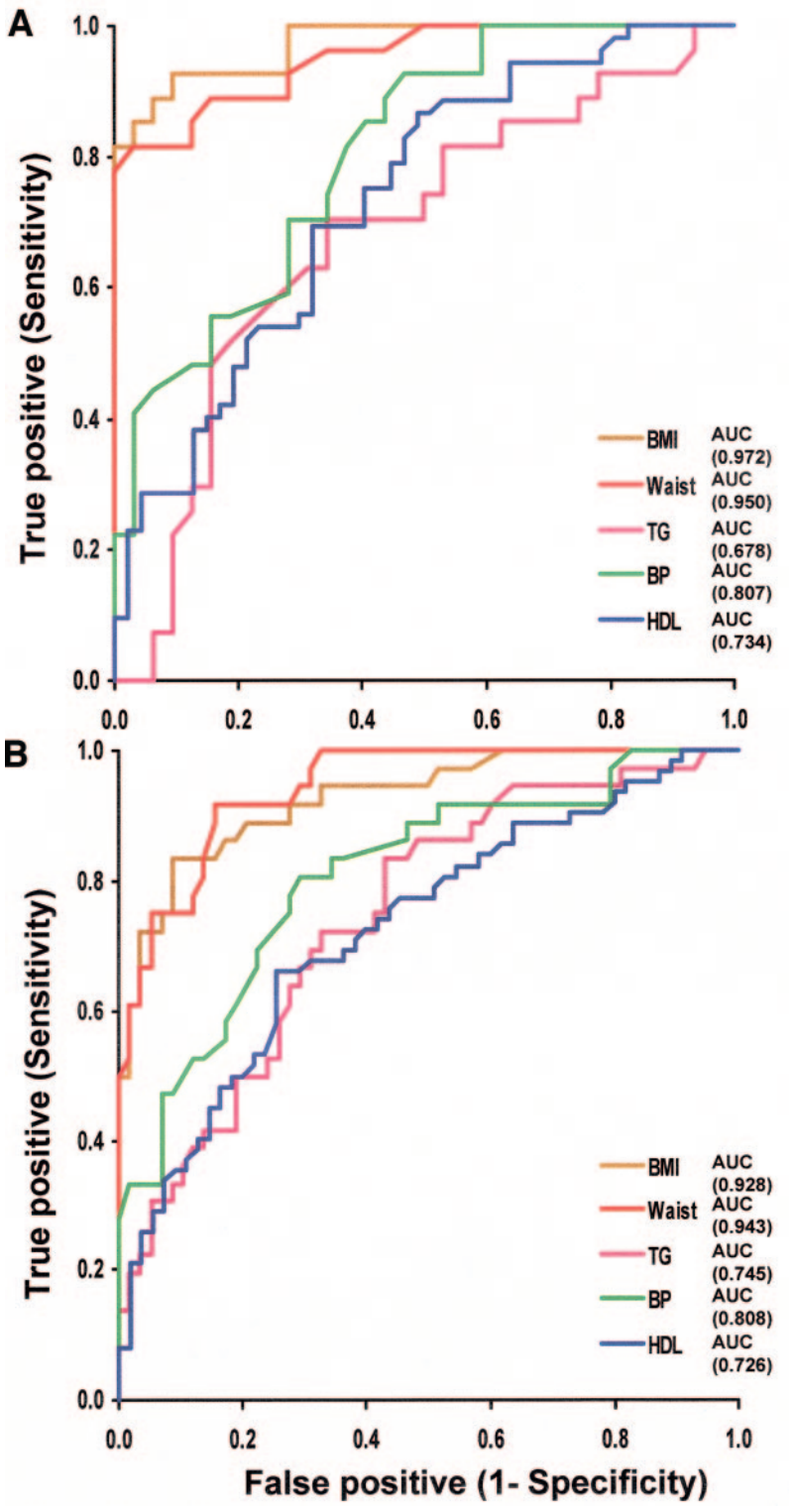

Figure 4—*ROC curves of individual components of metabolic syndrome as markers of insulin resistance. Insulin resistance was defined based on cutoffs of insulin sensitivity (lower 10th percentile) derived from the non-overweight group (cutoffs, black: 4.6 mg · kg^{-1} · min^{-1} per μU/ml; whites: 4.4 mg · kg^{-1} · min^{-1} per μU/ml). AUC, area under the curve; TG, triglycerides.*

insulin sensitivity independent of race. Given the simplicity of this measure relative to in vivo insulin sensitivity measurement, our findings suggest that adiponectin could potentially be added as a surrogate marker of insulin resistance in the aggregate criteria of metabolic syndrome in the research setting. However, additional studies are needed to define the tracking of adiponectin levels from childhood to adulthood and its predictive value for future CVD.

In conclusion, although our study has some weaknesses such as *1*) waist circumference was not obtained in all of our subjects and *2*) subjects with polycystic ovarian syndrome were included in the analyses, we have demonstrated that insulin resistance is significantly associated with the individual components of metabolic syndrome in black and white youth. Although in whites insulin resistance mediated in part via VAT is associated with the early manifestation of the atherosclerotic process through elevated biomarkers of endothelial dysfunction, this does not seem to be the case in blacks. It remains to be determined what underlies the racial differences in risk translation. We propose that the inherently lower abdominal adiposity and triglyceride levels in blacks may play a role. Longitudinal studies are needed to test these hypotheses.

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