ORIGINAL ARTICLE

Obesity and the Metabolic Syndrome in Children and Adolescents

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ABSTRACT

BACKGROUND

The prevalence and magnitude of childhood obesity are increasing dramatically. We examined the effect of varying degrees of obesity on the prevalence of the metabolic syndrome and its relation to insulin resistance and to C-reactive protein and adiponectin levels in a large, multiethnic, multiracial cohort of children and adolescents.

METHODS

We administered a standard glucose-tolerance test to 439 obese, 31 overweight, and 20 nonobese children and adolescents. Baseline measurements included blood pressure and plasma lipid, C-reactive protein, and adiponectin levels. Levels of triglycerides, high-density lipoprotein cholesterol, and blood pressure were adjusted for age and sex. Because the body-mass index varies according to age, we standardized the value for age and sex with the use of conversion to a z score.

RESULTS

The prevalence of the metabolic syndrome increased with the severity of obesity and reached 50 percent in severely obese youngsters. Each half-unit increase in the body-mass index, converted to a z score, was associated with an increase in the risk of the metabolic syndrome among overweight and obese subjects (odds ratio, 1.55; 95 percent confidence interval, 1.16 to 2.08), as was each unit of increase in insulin resistance as assessed with the homeostatic model (odds ratio, 1.12; 95 percent confidence interval, 1.07 to 1.18 for each additional unit of insulin resistance). The prevalence of the metabolic syndrome increased significantly with increasing insulin resistance (P for trend, <0.001) after adjustment for race or ethnic group and the degree of obesity. C-reactive protein levels increased and adiponectin levels decreased with increasing obesity.

CONCLUSIONS

The prevalence of the metabolic syndrome is high among obese children and adolescents, and it increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters.

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In 1988, Reaven and colleagues[1] described "the metabolic syndrome" as a link between insulin resistance and hypertension, dyslipidemia, type 2 diabetes, and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular disease[2] in adults. Recent studies suggest that the metabolic syndrome may originate in utero.[2,3]

Obesity, which is the most common cause of insulin resistance in children,[4] is also associated with dyslipidemia,[5] type 2 diabetes,[6] and long-term vascular complications.[7-9] In a sample of adolescents in the United States who were included in the third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, the prevalence of the metabolic syndrome was 6.8 percent among overweight adolescents and 28.7 percent among obese adolescents.[10] However, these rates may underestimate the current extent of the problem, because both the magnitude and the prevalence of childhood obesity have increased in the past decade.[11]

We examined the effect of different degrees of obesity in children on the prevalence of the metabolic syndrome and its relationship to insulin resistance. Because high C-reactive protein and interleukin-6 levels and low adiponectin levels are independent risk factors for atherosclerosis in obese, insulin-resistant adults,[12,13] we also examined the relationship between childhood obesity and these putative surrogate markers of future cardiovascular disease.

METHODS

STUDY POPULATION

We studied 439 obese children and adolescents beginning in 1999. Subjects were eligible if they were healthy, were between 4 and 20 years of age, and had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) that exceeded the 97th percentile for their age and sex.[14] Exclusion criteria were the known presence of diabetes and the use of medication that alters blood pressure or glucose or lipid metabolism. Parents provided information about race or ethnic group: 179 subjects were white (40.8 percent), 135 were black (30.8 percent), 120 were Hispanic (27.3 percent), and 5 subjects were classified as other. Twenty nonobese siblings of obese subjects (BMI, <85th percentile) and 31 overweight siblings (BMI, 85th to 97th percentile) were recruited as comparison groups. The Yale University School of Medicine human investigation committee approved the study. Written informed consent from parents and written assent from children (where appropriate) and adolescents were obtained.

PROCEDURES

The subjects consumed a diet containing at least 250 g of carbohydrates per day for three days before the study and refrained from vigorous physical activity. They were evaluated at 8 a.m., after a 12-hour, overnight fast. Their weight and height were measured, and their BMI was calculated. Blood pressure was measured three times while the subjects were seated, and the last two measurements were averaged for analysis. The physical examination included determination of the stage of puberty according to the criteria of Tanner.[15]

Baseline blood samples were obtained from subjects while they were fasting, with the use of an indwelling venous line for measurement of levels of glucose, insulin, lipids, adiponectin (in the 328 most recently enrolled subjects), C-reactive protein, and interleukin-6 (in the 293 most recently enrolled subjects). An oral glucose-tolerance test was then performed with the administration of 1.75 g of glucose per kilogram of body weight (maximal dose, 75 g).[16]

DEFINITIONS

The criteria we used to diagnose the metabolic syndrome were modified from those of the National Cholesterol Education Program's Adult Treatment Panel[17] and the World Health Organization.[18] Because body proportions normally change during pubertal development and may vary among persons of different races and ethnic groups, differences in waist-to-hip ratios are difficult to interpret in children. We therefore defined obesity on the basis of a threshold BMI z score of 2.0 or more, adjusted for age and sex. The subjects were then classified as moderately obese (a z score of 2.0 to 2.5) or severely obese (a z score above 2.5). Elevated systolic or diastolic blood pressure was defined as a value that exceeded the 95th percentile for age and sex.[19]

Abnormalities in the fasting levels of triglycerides and high-density lipoprotein (HDL) cholesterol were adjusted for age, sex, and race or ethnic group (>95th percentile for triglycerides; <5th percentile for HDL cholesterol).[20] Impaired glucose tolerance was defined as a glucose level greater than 140 mg per deciliter (7.8 mmol per liter) but less

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Table 1. Baseline Anthropometric and Metabolic Characteristics of the Study Cohort.*

Characteristic	Nonobese (N=20)	Overweight (N=31)	Moderately Obese (N=244)	Severely Obese (N=195)	P Value†	
					Adjusted	Unadjusted
Sex — no. (%)						
Female	10 (52)	19 (61)	162 (66)	98 (51)		
Male	9 (48)	12 (39)	81 (33)‡	93 (49)		
Age — yr						
Mean	11.7	11.9	12.8	11.3		
95% CI	10.5 to 12.9	10.8 to 13.1	12.5 to 13.1§	10.9 to 11.8		
Height — cm						
Mean	149.6	150.9	158.9	154.3		
95% CI	143.8 to 155.4	146.4 to 155.5	157.5 to 160.4	152.0 to 156.7		
Weight — kg						
Mean	41.9	56.9	85.6	100.2		
95% CI	37.1 to 46.7	51.1 to 62.8	83.2 to 88.1	95.4 to 105.1		
BMI						
Mean	18.4	24.5	33.4	40.6		
95% CI	17.4 to 19.4	23.1 to 25.9	32.8 to 34.0	39.5 to 41.7		
BMI z score						
Mean	0.02	1.52	2.29	2.78		
95% CI	–0.34 to 0.4	1.4 to 1.6	2.3 to 2.3	2.8 to 2.8		
Pubertal status — no. (%)						
Prepubertal	7 (37)	13 (42)	40 (16)	76 (40)		
Pubertal	12 (63)	18 (58)	203 (84)¶	115 (60)		
Race or ethnic group — no. (%)						
Black	4 (21)	2 (6)	68 (28)	67 (35)		
White	9 (47)	20 (64)	110 (45)	69 (36)		
Hispanic	6 (32)	9 (30)	65 (27)	55 (29)		
Glucose — mg/dl						
Total	87.4	86.8	90.5	90.2	0.04	0.06
	83.9 to 90.8	84.5 to 89.2	89.6 to 91.5	89.0 to 91.3		
Blacks						
Mean			91	89.9		
95% CI			89.0 to 93.0	87.9 to 91.9		
Whites						
Mean			90.3	88.6		
95% CI			88.8 to 91.7	86.6 to 90.6		
Hispanics						
Mean			90.4	92.4		
95% CI			88.5 to 92.4	90.4 to 94.2		
Insulin — μU/ml					<0.001	<0.001
Total						
Mean	10.3	14.6	31.3	38.6		
95% CI	8.0 to 13.2	11.8 to 18.2	29.2 to 33.3	34.8 to 42.4		
Blacks						
Mean			33.1	41.5		
95% CI			29.1 to 37.1	34.2 to 48.7		
Whites						
Mean			31.0	33.8		
95% CI			27.8 to 34.2	28.2 to 39.4		
Hispanics						
Mean			29.8	41.2		
95% CI			26.1 to 33.6	33.5 to 48.9		

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Table 1. (Continued.)

Characteristic	Nonobese (N=20)	Overweight (N=31)	Moderately Obese (N=244)	Severely Obese (N=195)	P Value†	
					Adjusted	Unadjusted
Insulin resistance‖					<0.001	<0.001
Total						
Mean	2.20	3.12	7.05	8.69		
95% CI	1.7 to 2.9	2.5 to 3.9	6.6 to 7.5	7.8 to 9.1		
Blacks						
Mean			7.53	9.41		
95% CI			6.58 to 8.5	7.61 to 11.2		
Whites						
Mean			6.94	7.49		
95% CI			6.2 to 7.7	6.2 to 8.8		
Hispanics						
Mean			6.77	9.37		
95% CI			5.8 to 7.8	7.6 to 11.2		
Triglycerides — mg/dl					<0.001	<0.001
Total						
Mean	48.4	83.1	104.6	96.5		
95% CI	42.5 to 54.6	68.7 to 100.5	96.5 to 112.2	90.1 to 102.5		
Blacks						
Mean			77	78		
95% CI			67 to 88	70 to 86**		
Whites						
Mean			129	109		
95% CI			116 to 144	98 to 121		
Hispanics						
Mean			99	106		
95% CI			87 to 114	95 to 120		
HDL cholesterol — mg/dl					<0.001	<0.001
Total						
Mean	58.5	46.7	41.1	39.9		
95% CI	52.3 to 64.7	42.0 to 51.3	39.9 to 42.3	38.6 to 41.3		
Blacks						
Mean			45.7	42.8**		
95% CI			43.1 to 48.3	40.1 to 45.6		
Whites						
Mean			39.8	38.7		
95% CI			38.2 to 41.4	36.9 to 40.6		
Hispanics						
Mean			38.3	38.5		
95% CI			36.2 to 40.3	36.3 to 40.7		
LDL cholesterol — mg/dl					0.57	0.41
Total						
Mean	92.2	95.5	98.1	97.3		
95% CI	77.2 to 107.2	84.1 to 106.9	94.1 to 102.1	93.7 to 100.9		
Blacks						
Mean			94.6	93.1		
95% CI			87.2 to 102.1	86.2 to 100.1		
Whites						
Mean			102.5	102.9		
95% CI			96.6 to 108.4	97.2 to 108.6		
Hispanics						
Mean			94.5	95.2		
95% CI			86.3 to 102.7	89.4 to 101.1		

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Table 1. (Continued.)

Characteristic	Nonobese (N=20)	Overweight (N=31)	Moderately Obese (N=244)	Severely Obese (N=195)	P Value†	
					Adjusted	Unadjusted
Systolic pressure — mm Hg					<0.001	<0.001
Total						
Mean	106	116	121	124		
95% CI	102 to 110	112 to 121	119 to 123	122 to 126		
Blacks						
Mean			125	124		
95% CI			122 to 127	120 to 127		
Whites						
Mean			121	128		
95% CI			119 to 124	124 to 131		
Hispanics						
Mean			117	120		
95% CI			114 to 120	116 to 125		
Impaired glucose tolerance — %					0.01	0.01
Total						
Mean	0	3.23	14.40	19.9		
95% CI	0 to 20	0 to 17	10.3 to 19.6	15.5 to 24.5		
Blacks			11.7	16.4		
Mean						
95% CI						
Whites			16.4	23.2		
Mean						
95% CI						
Hispanics			13.9	20.0		
Mean						
95% CI						
Adiponectin — μg/dl					0.001	0.01
Total						
Mean	9.6	8.0	6.7	5.8		
95% CI	6.1 to 15.3	6.0 to 10.6	6.2 to 7.3	5.3 to 6.5		
Blacks						
Mean			6.3	5.3		
95% CI			5.5 to 7.2	4.5 to 6.3		
Whites						
Mean			7.4	5.8		
95% CI			6.5 to 8.3	4.8 to 6.9		
Hispanics						
Mean			6.2	6.7		
95% CI			5.2 to 7.4	5.6 to 8.0		
CRP — mg/dl					<0.001	<0.001
Total						
Mean	0.01	0.05	0.13	0.33		
95% CI	0.001 to 0.03	0.03 to 0.09	0.10 to 0.16	0.27 to 0.40		
Blacks						
Mean			0.13	0.32		
95% CI			0.09 to 0.19	0.23 to 0.45		
Whites						
Mean			0.12	0.31		
95% CI			0.09 to 0.17	0.25 to 0.44		
Hispanics						
Mean			0.13	0.35		
95% CI			0.09 to 0.19	0.25 to 0.45		

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Table 1. (Continued.)

Characteristic	Nonobese (N=20)	Overweight (N=31)	Moderately Obese (N=244)	Severely Obese (N=195)	P Value†	
					Adjusted	Unadjusted
Interleukin-6 — pg/ml					<0.001	<0.001
Total						
Mean	0.92	0.99	1.80	2.45		
95% CI	0.32 to 2.58	0.64 to 1.53	1.58 to 2.05	2.05 to 2.94		
Blacks						
Mean			1.89	2.36		
95% CI			1.46 to 2.45	1.71 to 3.25		
Whites						
Mean			1.59	1.80		
95% CI			1.32 to 1.93	1.24 to 2.63		
Hispanics						
Mean			2.07	3.09		
95% CI			1.59 to 2.69	2.36 to 4.05		

* Obese subjects with a body-mass index (BMI) converted to a z score of 2.0 to 2.5 were classified as moderately obese, and subjects with a z score of more than 2.5 were classified as severely obese. One nonobese subject, one moderately obese subject, and three severely obese subjects whose reported race or ethnic group was not white, Hispanic, or black were excluded from the analysis. CI denotes confidence interval, HDL high-density lipoprotein, LDL low-density lipoprotein, and CRP C-reactive protein. To convert the values for glucose to millimoles per liter, multiply by 0.0005; to convert the values for insulin to picomoles per liter, multiply by 6; to convert the values for triglycerides to millimoles per liter, multiply by 0.01129; to convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† P values are for trend across all weight groups (unadjusted and adjusted for sex, pubertal stage, and race and ethnic group).

‡ P=0.001 for the comparison with severely obese subjects.

§ P<0.001 for the comparison with severely obese subjects.

¶ P<0.001 for the comparison with severely obese subjects, P=0.03 for the comparison with lean subjects, and P<0.001 for the comparison with overweight subjects.

‖ The data for insulin resistance are based on a homeostatic model (homeostatic model assessment: insulin resistance[22]). It is calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter), divided by 22.5. Scores ordinarily range from 0 to 15, with higher scores indicating greater insulin resistance.

** P<0.001 for the comparison with white subjects and with Hispanic subjects.

than 200 mg per deciliter (11.1 mmol per liter) at two hours.[21] Like adults, the children and adolescents in our study were classified as having the metabolic syndrome if they met three or more of the following criteria for age and sex: they had a BMI above the 97th percentile (z score, 2.0 or more), a triglyceride level above the 95th percentile, an HDL cholesterol level below the 5th percentile, systolic or diastolic blood pressure above the 95th percentile, and impaired glucose tolerance. The degree of insulin resistance was determined with the use of a homeostatic model (homeostatic model assessment: insulin resistance).[22] Scores ordinarily range from 0 to 15, with higher scores indicating greater insulin resistance, and are calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter), divided by 22.5.

BIOCHEMICAL ANALYSIS

Plasma glucose levels were measured with the use of the YSI 2700 STAT Analyzer (Yellow Springs Instruments), and lipid levels were measured with the use of an AutoAnalyzer (model 747–200, Roche–Hitachi). Plasma insulin and adiponectin levels were measured with the use of a radioimmunoassay (Linco Laboratories). C-reactive protein levels were measured with the use of an ultrasensitive assay (Kamiya Biomedical) (intraassay coefficient of variation, 1.24 percent; interassay coefficient of variation, 4.2 percent). Interleukin-6 levels were measured with the use of highly sensitive solid-phase enzyme-linked immunosorbent assay kits (R&D

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Systems) (lower limit of detection, 0.1 pg per milliliter; intraassay and interassay coefficients of variation, 3.3 percent and 3.6 percent, respectively).

STATISTICAL ANALYSIS

The data are expressed either as frequencies or as means with 95 percent confidence intervals. Distributions of continuous variables were examined for skewness and kurtosis and were logarithmically transformed, when appropriate. Geometric means are reported for insulin levels obtained from fasting subjects and for insulin resistance and triglyceride levels. Differences across weight categories, insulin-resistance categories, and racial or ethnic groups and between the sexes in the anthropometric, cardiovascular, and metabolic variables were assessed with the use of linear regression. Mantel–Haenszel chi-square statistics were used to evaluate trends in proportions across weight and insulin-resistance categories. Tests for departure from linear trend[23] were performed for analyses of differences in means and proportions across weight and insulin-resistance categories, with pairwise comparisons for both variables evaluated with the use of Holm's adjustment in the case of a significant departure from linearity.[24] When the few obese subjects with lean or overweight siblings who also participated in the study were excluded from the analysis, means and variances were unaltered, indicating a negligible effect of correlation between data on siblings. Thus, the data are presented without adjustment for the correlation of sibling data.

Principal-component factor analysis was used to investigate the relations among the correlated risk factors for the metabolic syndrome in 470 obese and overweight children. Extraction of the initial set of uncorrelated components was accomplished with the principal-factor method, and then orthogonal rotation of components was used to facilitate interpretation. Eight variables related to the metabolic syndrome were included in the factor analysis. The number of components retained was based on Scree plot analysis and Eigen values greater than 1 (with the components accounting for more of the total variance than any single variable). Factor loading — the product-moment correlation (a measure of linear association) between an observed variable and an underlying factor — was used to interpret the factor structure. Loadings are equivalent to Pearson correlation coefficients, with a higher loading indicating a stronger relation between a factor and an observed variable.[25] We defined factor loadings from 0.2 through 0.4 as indicating marginal correlations and loadings above 0.4 as indicating strong correlation. Multivariable logistic regression was performed to identify variables that were significantly related to the odds of having the metabolic syndrome. The results are reported as odds ratios with 95 percent confidence intervals. All analyses were performed with the use of SAS software (version 8.2, SAS Institute).

RESULTS

ANTHROPOMETRIC AND METABOLIC PHENOTYPE

Anthropometric and metabolic data are shown in Table 1. Values for glucose, insulin, insulin resistance, triglycerides, C-reactive protein, interleukin-6, and systolic blood pressure, as well as the prevalence of impaired glucose tolerance, increased significantly with increasing obesity, whereas HDL cholesterol and adiponectin levels decreased with increasing obesity (Table 1). Moderately and severely obese black subjects had lower triglyceride and higher HDL cholesterol levels than similar white and Hispanic subjects. The percentage of subjects with impaired glucose tolerance increased directly with the severity of obesity in subjects in all racial and ethnic groups, a trend that persisted after adjustment for sex, pubertal status, and race or ethnic group. The severity of obesity and the prevalence of the metabolic syndrome were strongly associated after adjustment for race and ethnic group ($P=0.009$) and for race and ethnic group and sex ($P=0.03$).

The overall prevalence of the metabolic syndrome was 38.7 percent in moderately obese subjects and 49.7 percent in severely obese subjects; no overweight or nonobese subject met the criteria for the metabolic syndrome. The prevalence of the metabolic syndrome in severely obese black subjects was 39 percent. When we analyzed our data according to the commonly accepted criteria of the National Cholesterol Education Program[26] (which are not specific to any race or ethnic group), the prevalence of the metabolic syndrome among severely obese black subjects was only 27 percent.

FACTOR ANALYSIS

As shown in Table 2 and Table 3, three factors were sufficient to explain correlations between variables — obesity and glucose metabolism, the degree of

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dyslipidemia, and blood pressure. The three factors explained 58 percent of the total variance in the data (27 percent of the variance was explained by the first factor, an additional 17 percent by the second factor, and another 14 percent by the third factor). The first factor was obesity and glucose metabolism, reflecting strong correlation with the z score for the body-mass index, insulin resistance, and fasting and two-hour plasma glucose levels. The second factor was dyslipidemia, reflecting a positive correlation of insulin resistance with the triglyceride level and a negative correlation of insulin resistance with the HDL cholesterol level. The third factor was blood pressure, reflecting a positive correlation with systolic and diastolic blood pressure. When the C-reactive protein level was incorporated into the analysis (for 293 subjects), it loaded significantly only with the obesity and glucose metabolism factor.

INSULIN RESISTANCE

To test the effect of insulin resistance on the prevalence of the metabolic syndrome, we categorized the subjects according to three insulin-resistance categories, using the 33rd and 66th percentiles as cutoffs, and race or ethnic group, with adjustment for the degree of obesity (Fig. 1). The prevalence of the metabolic syndrome increased significantly with increasing insulin resistance (P for trend, <0.001) after adjustment for race or ethnic background and obesity group. The prevalence was lower in black subjects than in white subjects (P<0.001) but not than in Hispanic subjects (P=0.20), and it was higher in severely obese subjects than in moderately obese subjects (P=0.03).

MULTIPLE LOGISTIC-REGRESSION ANALYSIS

For the multiple logistic-regression analysis of risk factors associated with the metabolic syndrome in

Table 2. Pearson Correlation Coefficients of Variables in the Analysis.

Variable	BMI z Score	Log-Transformed Triglycerides	HDL Cholesterol	Log-Transformed Insulin Resistance	Glucose		Blood Pressure	
					Baseline	At 2 Hr	Systolic	Diastolic
BMI z score								
Correlation coefficient	1.0	0.04	–0.14	0.31	0.08	0.12	0.13	–0.01
P value		0.33	0.001	<0.001	0.08	0.007	0.003	0.82
Log-transformed triglycerides								
Correlation coefficient	—	1.0	0.42	0.25	0.04	0.18	0.64	–0.01
P value			<0.001	<0.001	0.34	<0.001	0.16	0.76
HDL cholesterol								
Correlation coefficient	—	—	1.0	–0.25	–0.07	–0.11	–0.03	0.08
P value				<0.001	0.10	0.01	0.46	0.07
Log-transformed insulin resistance								
Correlation coefficient	—	—	—	1.0	0.39	0.35	0.19	0.09
P value					<0.001	<0.001	<0.001	0.04
Glucose								
Baseline								
Correlation coefficient	—	—	—	—	1.0	0.25	0.10	0.09
P value						<0.001	0.01	0.04
At 2 hr								
Correlation coefficient	—	—	—	—	—	1.0	0.09	–0.01
P value							0.03	0.86
Blood pressure								
Systolic								
Correlation coefficient	—	—	—	—	—	—	1.0	0.32
P value								<0.001
Diastolic								
Correlation coefficient	—	—	—	—	—	—	—	1.0
P value								

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overweight and obese children and adolescents, we incorporated age, sex, z score for BMI, race or ethnic group, and insulin-resistance level into the model. The overall significance of the model was P<0.001. Increasing insulin-resistance levels according to the homeostatic-model assessment were significantly related to the risk of the metabolic syndrome (odds ratio for each increase of one unit, 1.12; 95 percent confidence interval, 1.07 to 1.18). Each half-unit increase in the z score for the body-mass index (one half of 1 SD) was associated with a significant increase in the risk of the metabolic syndrome (odds ratio, 1.55; 95 percent confidence interval, 1.16 to 2.08). White subjects had a higher risk of the metabolic syndrome than black subjects (odds ratio, 2.20; 95 percent confidence interval, 1.35 to 3.59); there was no significant difference in risk between Hispanic subjects and black subjects. Girls were at lower risk for the metabolic syndrome than boys (odds ratio, 0.59; 95 percent confidence interval, 0.39 to 0.89). When the z score for the body-mass index was excluded, the odds ratios associated with each unit of increase in insulin resistance, female sex, and white race as compared with black race did not change significantly.

Table 3. Principal-Factor Analysis and Oblique Analysis of the Whole Cohort of Obese and Overweight Children and Adolescents, According to Risk Factors for the Metabolic Syndrome.*

Variable	Factor		
	Obesity and Glucose Metabolism	Dyslipidemia	Blood Pressure
	correlation coefficient		
BMI z score	0.44	0.13	0.06
Log-transformed triglycerides	0.09	0.83	0.04
HDL cholesterol	–0.13	–0.82	0.06
Log-transformed insulin resistance	0.76	0.27	0.15
Log-transformed glucose			
Baseline	0.72	–0.14	0.07
At 2 hr	0.67	0.10	–0.06
Blood pressure			
Systolic	0.15	0.09	0.79*
Diastolic	0.01	–0.09	0.83*
	percent		
Variance	27	17	14
Cumulative proportion of variance†	27	44	58

* Factor loading is the product-moment correlation (a measure of linear association) between an observed variable and an underlying factor. Strong loading was defined as a value greater than 0.4, and marginal loading as a value from 0.2 to 0.4.

† The first value in the row gives the proportion of variance (the degree of spread in the data set) explained by obesity and glucose metabolism; the second value, the proportion explained by obesity and glucose metabolism plus that explained by dyslipidemia; and the third value, the proportion explained by the previous two factors plus blood pressure.

PROINFLAMMATORY AND ANTIINFLAMMATORY MARKERS AND INSULIN RESISTANCE

C-reactive protein levels (Fig. 2A) were significantly related to the degree of obesity (P<0.001) but not to the level of insulin resistance (P=0.12). The levels tended to rise with the number of components of the metabolic syndrome in this cohort, but the trend did not reach statistical significance.

Adiponectin levels decreased with increasing obesity (Table 1). When the subjects were stratified according to obesity group and insulin-resistance category (Fig. 2B), the adiponectin levels were significantly associated with the obesity category (P=0.04) and insulin-resistance category (P=0.005); the adiponectin levels were lowest in subjects with the highest level of insulin resistance. There was an interaction between obesity and insulin resistance, but it was not statistically significant (P=0.07). After stratification according to obesity group, the effect of insulin-resistance category was evident in the moderately obese group; subjects in the highest category of insulin resistance had significantly lower adiponectin levels than those in the middle and low categories (P=0.04 and P=0.002, respectively, with Holm's adjustment). In contrast, adiponectin levels in the severely obese group did not vary significantly according to the insulin-resistance category. Adiponectin levels were negatively correlated with C-reactive protein levels (R=–0.18, P=0.005).

Interleukin-6 levels rose significantly with the degree of obesity (Table 1) and were correlated with C-reactive protein levels (R=0.37, P<0.001) but not with the degree of insulin resistance. The relation between interleukin-6 and C-reactive protein levels persisted after adjustment for the z score for the body-mass index (R=0.29, P<0.001).

THE METABOLIC SYNDROME PHENOTYPE AFTER TWO YEARS OF FOLLOW-UP

Seventy-seven subjects underwent a second comprehensive assessment after a mean (±SD) interval of 21.5±10.5 months. Twenty-four of the 34 subjects in this group who had met the criteria for the metabolic syndrome initially met these criteria at the time of the second evaluation as well. The 10 who did not meet the criteria on follow-up were

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among the subjects who had a lower BMI initially (z score, 2.42±0.07 vs. 2.62±0.06; P=0.06), had gained less weight (3.74±2.6 kg vs. 11.93±2.9 kg, P=0.05), and tended to have decreased insulin resistance (a reduction from 9.68±1.14 to 7.54±0.82, P=0.07). The syndrome developed over time in 16 of 43 children who did not have the metabolic syndrome at the time of the first evaluation. The baseline z score for the body-mass index in these 16 subjects was similar to that in the 10 subjects who had improvement during follow-up (2.39±0.11 and 2.42±0.07, respectively; P=0.86), yet they gained significantly more weight (16.91±4.4 kg vs. 3.74±2.6 kg, P=0.02). In eight subjects, all of whom had impaired glucose tolerance at the first evaluation, type 2 diabetes developed during follow-up.

DISCUSSION

Our findings suggest that the metabolic syndrome is far more common among children and adolescents than previously reported and that its prevalence increases directly with the degree of obesity. Moreover, each element of the syndrome worsens with increasing obesity — an association that is independent of age, sex, and pubertal status. Our study shows that, as in obese adults,[27] insulin resistance in obese children is strongly associated with specific adverse metabolic factors. C-reactive protein and interleukin-6 levels, which are putative biomarkers of inflammation and potential predictors of adverse cardiovascular outcomes, rose with the degree of obesity, whereas adiponectin levels, a biomarker of insulin sensitivity, decreased.

The degree of obesity in children and adolescents has important clinical implications, because the risk of death from all causes among adults with severe obesity is twice that among moderately obese adults.[28] Data on the prevalence of severe obesity in children and adolescents do not exist, to our knowledge. Our results show a significant adverse effect of worsening obesity on each component of the metabolic syndrome, underscoring the deleterious effect of increasing BMI in this age group.

We slightly modified the criteria used to assess adults for use in defining the metabolic syndrome in children and adolescents. An increase in waist circumference is used to define central obesity in adults. Although waist circumference in children is a good predictor of visceral adiposity,[29] it may not be useful for detecting differences in body proportions that are related to puberty and variations among racial and ethnic groups,[30] and no normative values exist for children and adolescents. In studies of lean and obese adolescents, we found

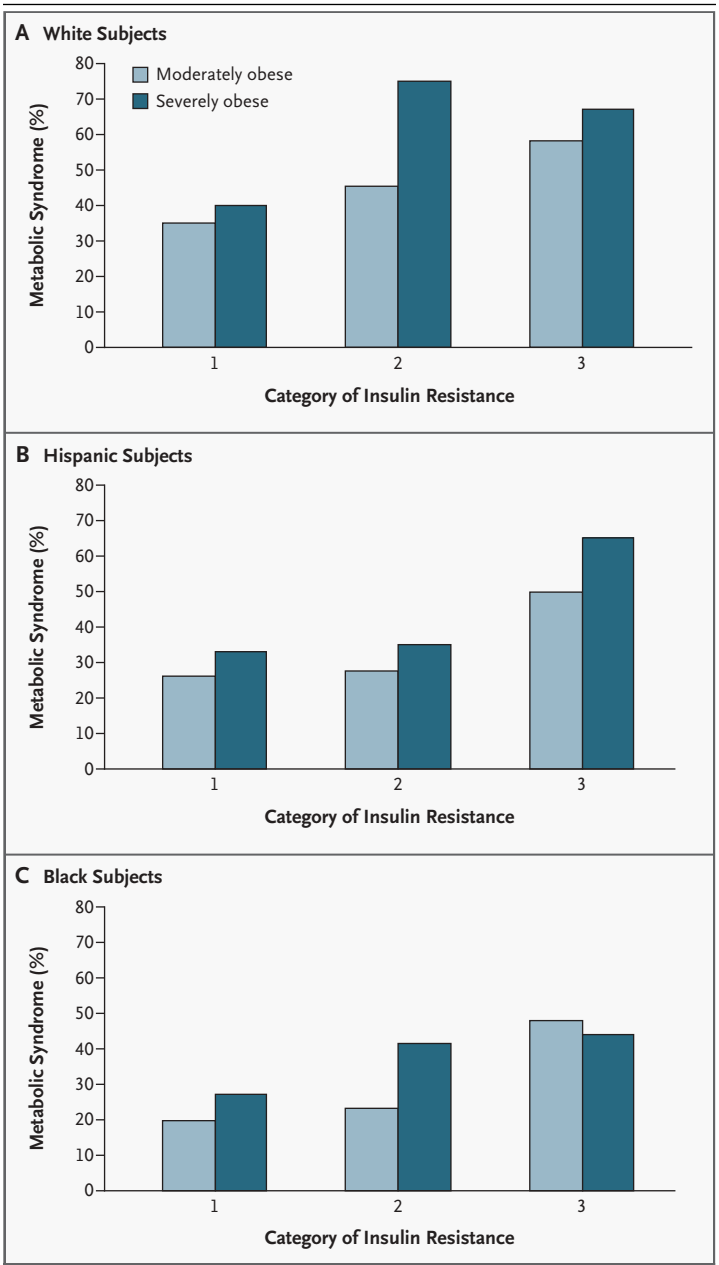


Figure 1. Effect of Insulin Resistance on the Prevalence of the Metabolic Syndrome in White Subjects (Panel A), Hispanic Subjects (Panel B), and Black Subjects (Panel C), According to the Degree of Obesity.

Subjects were grouped into three categories of insulin resistance, with cutoffs at the 33rd and 66th percentiles.

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that the BMI correlated strongly with the visceral lipid depot (R=0.72, P<0.001) (data not shown). The BMI correlates with blood pressure better than does waist circumference and performs similarly for dyslipidemia.[31] Therefore, we chose a z score of 2.0 or more for the BMI as a criterion for the metabolic syndrome. The obese cohort was divided on the basis of the 50th percentile (a z score of 2.5) in order to classify the patients as moderately obese or severely obese. We selected impaired glucose tolerance as a criterion for the metabolic syndrome, because impaired fasting glucose (levels above 100 mg per deciliter [5.6 mmol per liter]) is rare in childhood. Blood pressure and fasting lipid levels were compared with population norms adjusted for age and sex.

When black subjects and subjects belonging to other racial and ethnic groups were analyzed according to the same criteria for serum lipid levels, the prevalence of the metabolic syndrome was substantially lower than it was among the white subjects. However, when the analysis was performed with lipid thresholds specific to black subjects (who have a more favorable lipid profile than white subjects in the same age group), the prevalence of the metabolic syndrome and the effect of obesity were similar to those in the white and Hispanic subjects. Thus, the use of criteria specific to race or ethnic group for the metabolic syndrome in children appears to be warranted. The rates of prevalence of the metabolic syndrome according to our criteria were higher than the rates reported by Cook et al.,[10] which may be explained in part by a greater degree of obesity in our cohort.

In adults, insulin resistance "drives" the processes underlying the metabolic syndrome.[32] When adult populations are stratified according to the degree of insulin resistance, as the children were in our study, the prevalence of the metabolic syndrome increases directly with insulin resistance.[33] Our factor analysis showed strong loading of insulin resistance to the obesity and glucose metabolism factor and moderate loading to the dyslipidemia factor, indicating a component of insulin resistance in two of three factors that account for the majority of the variance. The importance of insulin resistance in the metabolic syndrome is also supported by the results of multiple logistic-regression analysis with the use of insulin resistance as an independent factor and adjustment for the effects of other factors. These data suggest that pathophysiological mechanisms related to the metabolic syndrome in adults are already operative in childhood.

Berenson et al. reported a clustering of components of the metabolic syndrome with coronary and aortic atherosclerosis in young adults.[8] We examined the effects of childhood obesity on the C-reactive protein level, which is a biomarker of the inflammation associated with adverse cardiovascular outcomes[34,35] and of altered glucose metabolism.[36] In our cohort, C-reactive protein levels tended to rise with increases in the z score for

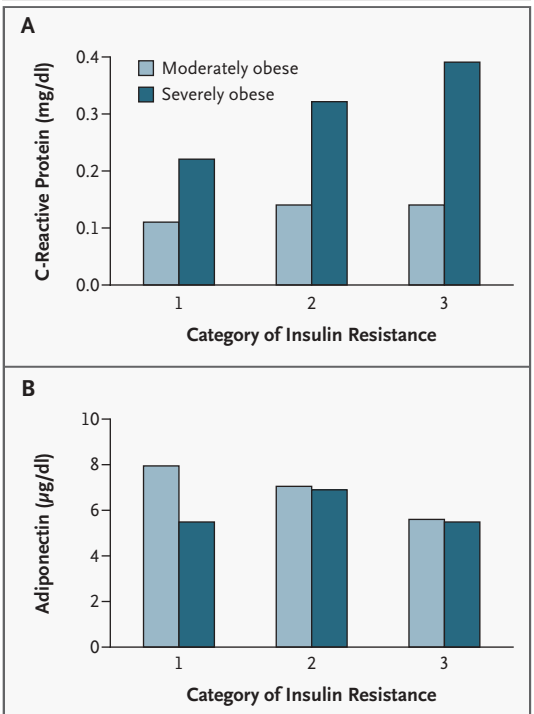


Figure 2. C-Reactive Protein and Adiponectin Levels According to the Degree of Obesity and the Insulin-Resistance Category.

Panel A shows C-reactive protein levels. P<0.001 for the association with the obesity group, and P=0.12 for the association with insulin-resistance category. P=0.64 for the interaction between the obesity group and the insulin-resistance category. Panel B shows adiponectin levels. P=0.04 for the association with the obesity group, and P=0.005 for the association with the insulin-resistance category. P=0.07 for the interaction between the obesity group and the insulin-resistance category. After stratification according to the obesity group, the effect of the insulin-resistance category was evident in moderately obese subjects; those in the highest category of insulin resistance had significantly lower adiponectin levels than those in the middle and low categories (P=0.04 and P=0.002, respectively, with Holm's adjustment).

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the body-mass index — a finding similar to that in another pediatric sample.[37] Although these levels were at the high end of the normal range, such levels have been associated with adverse outcomes.[38] The influence of the z score for the BMI on C-reactive protein levels suggests that the degree of low-grade inflammation may increase as children become more obese. However, C-reactive protein levels did not correlate significantly with insulin resistance or with the metabolic syndrome, suggesting that an underlying inflammation may be an additional factor contributing to adverse long-term cardiovascular outcomes in this population.

We also measured interleukin-6, a well-known regulator of hepatic production of C-reactive protein. Interleukin-6 levels increased with the degree of obesity. C-reactive protein and interleukin-6 levels were strongly related, even after adjustment for the degree of obesity. Adiponectin, apart from being a biomarker of insulin sensitivity, has been implicated as having an important role in preventing atheromatous plaques. In contrast to C-reactive protein levels, adiponectin levels tended to drop with increases in the z score for the BMI. Low levels of this adipocytokine have been shown to increase the risk of cardiovascular disease.[39] Both C-reactive protein and interleukin-6 showed a reciprocal trend with increasing obesity, suggesting a potentially significant effect of severe adiposity on adverse cardiovascular outcomes.

Preliminary follow-up of the subjects in the present study suggested that the metabolic syndrome phenotype persists over time and tends to progress clinically. In a relatively short period, full-blown type 2 diabetes developed in eight subjects who met the criteria for the metabolic syndrome. The development of type 2 diabetes in obese adolescents has been well documented. However, a dramatic increase in the incidence of type 2 diabetes may represent only the tip of the iceberg and may herald the emergence of an epidemic of advanced cardiovascular disease due to the synergistic effects of other components of the metabolic syndrome, as well as chronic low-grade inflammation, as obese adolescents become obese young adults.

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REFERENCES

1. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
2. Levitt NS, Lambert EV. The foetal origins of the metabolic syndrome — a South African perspective. Cardiovasc J S Afr 2002; 13:179-80.
3. Ozanne SE, Hales CN. Early programming of glucose-insulin metabolism. Trends Endocrinol Metab 2002;13:368-73.
4. Caprio S. Insulin resistance in childhood obesity. J Pediatr Endocrinol Metab 2002;15:Suppl 1:487-92.
5. Goran MI, Gower BA. Abdominal obesity and cardiovascular risk in children. Coron Artery Dis 1998;9:483-7.
6. Arslanian S. Type 2 diabetes in children: clinical aspects and risk factors. Horm Res 2002;57:Suppl 1:19-28.
7. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992;327:1350-5.
8. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998; 338:1650-6.
9. Steinberger J, Daniels SR. Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American Heart Association scientific statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Circulation 2003; 107:1448-53.
10. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med 2003;157:821-7.
11. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986-1998. JAMA 2001;286:2845-8.
12. Blake GJ, Ridker PM. Inflammatory biomarkers and cardiovascular risk prediction. J Intern Med 2002;252:283-94.
13. Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
14. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Advanced data from vital and health statistics. No. 314. Hyattsville, Md.: National Center for Health Statistics, 2000: 1-27. (DHHS publication no. (PHS) 2000-1250 0-0431.)
15. Tanner JM. Growth at adolescence: with a general consideration of the effects of hereditary and environmental factors upon growth and maturation from birth to maturity. 2nd ed. Oxford, England: Blackwell Scientific, 1962.
16. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002;346:802-10. [Erratum, N Engl J Med 2002;346:1756.]
17. Third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, Md.: National Heart, Lung, and Blood Institute, May 2001. (NIH publication no. 01-3670.)

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18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. 1. Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
19. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. Pediatrics 1996;98:649-58.
20. NGHS Coordinating Center. NHLBI Growth and Health Study (NGHS) data monitoring report. Baltimore: Maryland Medical Research, 1998.
21. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1999;22:Suppl 1:S5-S19.
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
23. Altman DG. Practical statistics for medical research. New York: Chapman & Hall, 1991.
24. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65-70.
25. Cureton EE, D'Agostino RB. Factor analysis: an applied approach. Hillside, N.J.: L. Erlbaum, 1983.
26. National Cholesterol Education Program. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Bethesda, Md.: National Heart, Lung, and Blood Institute, September 1991. (NIH publication no. 91-2732.)
27. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998;47:1643-9.
28. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097-105.
29. Goran MI. Visceral fat in prepubertal children: influence of obesity, anthropometry, ethnicity, gender, diet, and growth. Am J Hum Biol 1999;11:201-7.
30. Yanovski JA, Yanovski SZ, Filmer KM, et al. Differences in body composition of black and white girls. Am J Clin Nutr 1996;64:833-9.
31. Cook S, Auinger P, Daniels S. What best predicts medical complications of obesity? BMI, waist circumference or both. Obes Res 2003;11:Suppl:A27-A28. abstract.
32. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990;263:2893-9.
33. Abbasi F, Brown BW Jr, Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 2002;40:937-43.
34. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999;99:237-42.
35. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9. [Erratum, N Engl J Med 1997;337:356.]
36. Tan KC, Wat NM, Tam SC, Janus ED, Lam TH, Lam KS. C-reactive protein predicts the deterioration of glycemia in Chinese subjects with impaired glucose tolerance. Diabetes Care 2003;26:2323-8.
37. Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2003;108:1053-8.
38. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805-12. [Erratum, J Clin Invest 2003;112:299.]
39. Zietz B, Herfarth H, Paul G, et al. Adiponectin represents an independent cardiovascular risk factor predicting serum HDL-cholesterol levels in type 2 diabetes. FEBS Lett 2003;545:103-4.

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