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Homeostasis model assessment of insulin resistance*body mass index interactions at ages 9 to 10 years predict metabolic syndrome risk factor aggregate score at ages 18 to 19 years: a 10-year prospective study of black and white girls

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Abstract

If homeostasis model assessment of insulin resistance (HOMA-IR) interactions with obesity (body mass index [BMI]) at ages 9 to 10 years predict aggregate metabolic syndrome risk factors at ages 18 to 19 years, this would identify novel avenues for primary prevention of metabolic syndrome. Our hypothesis was that HOMA-IR*BMI interactions at ages 9 to 10 years would predict aggregate metabolic syndrome risk factor *z* scores at ages 18 to 19 years in prospective studies of a biracial population of girls. Two centers in the National Heart, Lung, and Blood Institute Growth and Health Study measured serum insulin and glucose at ages 9 to 10 years and 5 metabolic syndrome risk factors at ages 18 to 19 years (triglyceride, high-density lipoprotein cholesterol, systolic/diastolic blood pressure, waist circumference, and glucose). Studies in Cincinnati, OH, included girls from public and parochial schools in the inner city, within-city residential neighborhoods, and suburban areas; and those in Washington, DC, included girls from a health maintenance organization. Girls (194 white, 281 black) were studied first at ages 9 to 10 years, then at ages 18 to 19 years. We assessed HOMA-IR*BMI interactions at ages 9 to 10 years with race-specific *z* scores for 5 metabolic syndrome risk factors at ages 18 to 19 years. The lowest summed *z* score (mean ± SD) was observed for subjects in the lowest tertiles for both HOMA-IR and BMI (−1.15 ± 2.05), and the highest *z* score (2.58 ± 3.11) was for subjects in the highest tertiles for both HOMA-IR and BMI ($P < .0001$). For the top BMI tertile, there was a progressive increase in *z* score (increasing risk of metabolic syndrome) as HOMA-IR increased. Interaction of BMI with HOMA-IR at ages 9 to 10 years predicts aggregate metabolic risk score at ages 18 to 19 years, with progressive risk increments within the top BMI tertile as HOMA-IR increases, opening avenues for intervention to reduce both BMI and HOMA-IR at ages 9 to 10 years as a primary approach to prevention of metabolic syndrome at ages 18 to 19 years.

1. Introduction

Measures of obesity (body mass index [BMI], in kilograms per square meter) and insulin resistance (IR) in childhood predict the development of the metabolic syndrome in adulthood [1,2]. In the Young Finns Study [2], baseline insulin was higher in children who subsequently developed the metabolic syndrome. The Bogalusa Heart Study [3] followed 718 children from ages 8 to 17 years with baseline insulin and BMI measurements for an average of 11.6 years, finding that the children in the top quartile of BMI and insulin were 11.7 and 3.6 times more likely to develop metabolic syndrome as adults than children in the bottom quartile for BMI and insulin [3]. High childhood BMI was associated in the cohort with adult metabolic syndrome after adjusting for childhood insulin levels [3], but adjustment for childhood BMI eliminated the predictive relationship of childhood IR to adult metabolic syndrome [3]. Cruz et al [4] examined the insulin sensitivity–metabolic syndrome associations in obese Hispanic 8- to 13-year–old children. Insulin sensitivity was determined by the frequently sampled intravenous glucose tolerance test. After adjustment for

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adiposity, Cruz et al [4] found that insulin sensitivity was 62% lower in overweight youth with the metabolic syndrome than in overweight youth without the metabolic syndrome. Cruz et al [4] also reported that, in multivariate regression analysis, insulin sensitivity was independently and negatively related to triglycerides and blood pressure and positively related to high-density lipoprotein cholesterol (HDL-C). Cruz et al [4] concluded that the effects of adiposity on lipids and blood pressure (components of the metabolic syndrome) were mediated via IR. Altogether, obesity coupled with IR is a major contributor to the development of metabolic syndrome in childhood [1,4].

The prevalence of the metabolic syndrome is higher in obese than normal-weight children/adolescents regardless of the definition of metabolic syndrome used [5,6], and development of metabolic syndrome is accelerated by increasing obesity [7,8]. In addition, familial associations appear to influence the appearance and development of the metabolic syndrome. For example, maternal waist circumference predicts metabolic syndrome in their offspring [9].

An ancillary project of the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), a 10-year cohort study [10] of the development of obesity in black and white adolescent girls and its effects on cardiovascular disease risk factors, offered an opportunity to evaluate whether and to what degree interactions between preteen HOMA-IR and BMI were predictors of adolescent metabolic syndrome at ages 18 to 19 years. In the current study, our hypothesis was that HOMA-IR*BMI interactions at ages 9 to 10 years would predict aggregate metabolic syndrome risk at ages 18 to 19 years in prospective studies of a biracial population of girls. We further hypothesized that the relative contributions of HOMA-IR would be most marked in children characterized by upper tertile BMI.

2. Patients and methods

2.1. Study design

The NGHS clinical centers in Cincinnati, OH, and Washington, DC, measured fasting insulin and glucose levels at ages 9 to 10 years and 10 years later (Tables 1 and 2) [11]. Additional measures at ages 9 to 10 years and 10 years later included fasting lipid profile and systolic and diastolic blood pressure as well as weight, height, and waist circumference [11].

Race was self-declared; and as per the NGHS protocol [10], enrollment was restricted to racially concordant households, that is, to girls who said they were black or white and whose parents or guardians said that they were black or white, respectively. The Cincinnati, OH, clinic recruited girls from public and parochial schools in the inner city, within-city residential neighborhoods, and suburban areas; the Washington, DC, clinic recruited girls from a health maintenance organization. Procedures followed were in accordance with the ethical standards of the Institutional Review Boards of the 2 centers, who approved the study. Signed informed consent was obtained from the girls' parents or guardians and assent from the girls.

2.2. Clinical measures

In NGHS, obesity was assessed annually according to a standard protocol [10] using the BMI (in kilograms per square meter) as recommended by several expert panels [12,13]. In addition, beginning in year 2, waist circumference was measured at the minimum waist as an indicator of fat patterning. Pubertal maturation was visually assessed by a modification of Tanner staging to include areolar development instead of breast development [14] by trained, certified staff. Blood pressure (annually) and fasting blood lipids (biannually) were measured following a standard protocol [10]. Insulin and glucose levels were measured after an overnight fast (≥8 hours) using the Michigan Diabetes Research and Training Center (Ann Arbor) in year 1 (ages 9-10 years) and the Endocrine Laboratory at the University of Cincinnati/Children's Medical Center in year 10 (ages 18-19 years). Both insulin assays used a competitive protein-binding radioimmunoassay. Glucose was measured at year 1 using a hexokinase reagent (Boehringer, Mannheim, Germany) and at year 10 using the glucose oxidase method with the Hitachi 704 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Coefficients of variation ranged from 5% to 11% for insulin and 2% to 7% for glucose in year 1 and were 9% and 4%, respectively, in year 10. Homeostasis model assessment (HOMA-IR), which correlates with estimates of IR measured by the euglycemic clamp technique, was used as an index of IR [15]. Although the HOMA-IR measure is less accurate than the euglycemic clamp method, in large epidemiologic studies, it is a reasonable alternative to the complicated clamp method that requires continuous

Table 1
Mean (±SD) and median age, BMI, insulin, glucose, and HOMA-IR for all girls (races combined) and by race at study entry at ages 9 to 10 years

At study entry at ages 9-10 y	All girls (N = 475)	White girls (n = 194)	Black girls (n = 281)	*P* (Wilcoxon)
Age (y)	10.0 ± 0.5, 10.1	9.9 ± 0.5, 9.9	10.1 ± 0.5, 10.1	<.0001
BMI (kg/m^2)	18.6 ± 3.9, 17.6	17.4 ± 3.0, 16.7	19.4 ± 4.3, 18.3	<.0001
Insulin (μU/mL)	13.1 ± 10.9, 10.5	10.2 ± 9.4, 8.2	15.1 ± 11.4, 12.4	<.0001
Glucose (mg/dL)	93.5 ± 6.4, 93.0	93.3 ± 6.0, 93.0	93.6 ± 6.6, 93.0	.87
HOMA-IR	3.12 ± 2.76, 2.41	2.43 ± 2.45, 1.87	3.60 ± 2.87, 2.92	<.0001
Waist circumference (cm) at ages 10-11 y	64.9 ± 9.1, 62.9	62.2 ± 7.5, 60.5	66.7 ± 9.6, 64.6	<0.0001

Table 2
Mean (±SD) and median age, BMI, insulin, glucose, HOMA-IR, and metabolic syndrome components: triglycerides, HDL-C, systolic and diastolic blood pressure, waist circumference, fasting serum glucose, and metabolic syndrome *z* score for all girls (races combined) and by race at ages 18 to 19 years

At 10-y follow-up	All girls (N = 475)	White girls (n = 194)	Black girls (n = 281)	*P* (Wilcoxon)
Age (y)	19.0 ± 0.6, 19.0	18.9 ± 0.6, 18.9	19.1 ± 0.6, 19.1	<.0001
BMI (kg/m^2)	25.4 ± 6.8, 23.1	23.3 ± 4.8, 21.9	26.8 ± 7.6, 24.4	<.0001
Insulin (μU/mL)	10.9 ± 9.7, 8.0	8.4 ± 7.6, 7.0	12.6 ± 10.6, 10.0	<.0001
Glucose (mg/dL)	87.5 ± 11.8, 86.0	86.1 ± 7.6, 86.0	88.4 ± 13.8, 87.0	.015
HOMA IR (IR)	2.48 ± 2.86, 1.75	1.83 ± 1.80, 1.41	2.94 ± 3.34, 2.13	<.0001
Triglyceride (mg/dL)	80.3 ± 42.9, 69.0	96.3 ± 53.4, 86.0	69.2 ± 29.1, 62.0	<.0001
HDL-C (mg/dL)	52.3 ± 11.3, 50.0	50.6 ± 10.7, 49.0	53.4 ± 11.6, 51.0	.011
Systolic blood pressure (mm Hg)	108.5 ± 8.8, 108	106.3 ± 7.7, 106.0	110.0 ± 9.3, 109.0	<.0001
Diastolic blood pressure (mm Hg)	66.3 ± 9.2, 67.0	65.4 ± 9.1, 65.0	67.0 ± 9.3, 67.0	.052
Waist circumference (cm)	76.5 ± 13.3, 72.1	73.3 ± 10.0, 70.8	78.8 ± 14.7, 74.2	<.0001
Metabolic syndrome score	0.44 ± 2.91, 0.051	0.40 ± 2.91, 0.15	0.46 ± 2.91, 0.032	.96
With metabolic syndrome (glucose ≥100 mg/dL) (n [%])	20/475 (4.2%)	9/194 (4.6%)	11/281 (3.9%)	$\chi^2 = 0.15$, $P = .70$
With metabolic syndrome (glucose ≥110 mg/dL) (n [%])	18/475 (3.8%)	8/194 (4.1%)	10/281 (3.6%)	$\chi^2 = 0.10$, $P = .75$

intravenous administration of insulin and glucose for 3 hours for calculation of insulin sensitivity [16]. Huang et al [17] studied HOMA-IR in white and African American children and concluded that "... a modified HOMA equation accurately predicted insulin sensitivity, but its utility is similar to fasting insulin alone."

2.3. Statistical analyses

Because the measured variables in Tables 1 and 2 were not normally distributed by the Kolmogorov-Smirnov test, differences between black and white girls were assessed using the Wilcoxon nonparametric test.

Race-specific *z* scores were used to summarize the 5 candidate disorders that define the metabolic syndrome by at least 3 of the 5 conditions [18]: triglycerides of at least 150 mg/dL, HDL-C less than 50 mg/dL in women, systolic blood pressure of at least 135 mm Hg/diastolic blood pressure of at least 85 mm Hg, waist circumference of at least 88 cm, and fasting glucose of at least 110 mg/dL. First, each of the 6 variables was standardized to a mean of zero and variance of 1 (*z* score), separately by race. The higher of the systolic blood pressure *z* score or the diastolic blood pressure *z* score was used as *z* score for blood pressure, and then the 5 *z* scores were summed for each person. Because low HDL (<50 mg/dL in women) is a risk factor for metabolic syndrome [18], in our aggregation of *z* scores for metabolic syndrome, we multiplied all HDL *z* scores by −1. The summation of *z* scores (Fig. 1, Table 3) was used as a measure of aggregate risk for metabolic syndrome.

We defined metabolic syndrome in 2 ways, conventionally including a fasting glucose cut point of at least 110 mg/dL [18] or at least 100 mg/dL as one of the 5 components of the metabolic syndrome. To examine the relationship between metabolic syndrome and the summation of *z* scores, stepwise logistic regression was used with metabolic syndrome (yes/no) as dependent variable, and age, race, and summation of *z* scores as explanatory variables. The area under the receiver operating characteristic curve (AUR) from the resultant model was then calculated.

To examine relationships between BMI and HOMA-IR at ages 9 to 10 years and metabolic syndrome *z* score at ages 18 to 19 years, the girls in the study cohort were categorized into tertiles of BMI and HOMA-IR by ages 9 to 10 years (Fig. 1). The metabolic syndrome *z* score at ages 18 to 19 years was compared among 3 BMI tertiles and among 9 groups (3 tertiles of BMI*3 tertiles of HOMA-IR at ages 9-10 years) using analysis of variance, adjusted for age and for maturation stage at ages 9 to 10 years, for races combined (Fig. 1).

To examine the relationship between conventional metabolic syndrome and the status of 9 groups by entry BMI and HOMA-IR tertiles, stepwise logistic regression was used with metabolic syndrome at ages 18 to 19 years

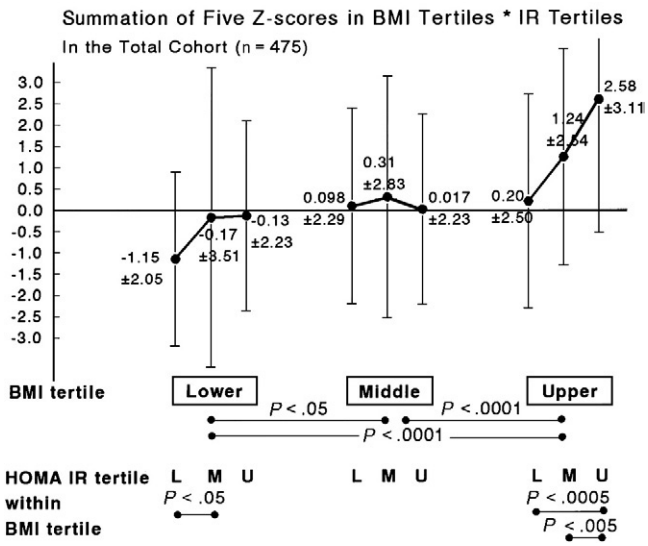

Fig. 1. Race-specific metabolic syndrome aggregate *z* score (mean ± SD) at ages 18 to 19 years for the total cohort, categorized in 9 groups (3 tertiles of BMI*3 tertiles of HOMA-IR at ages 9-10 years), and comparisons among 3 tertiles of BMI and among 3 tertiles of HOMA-IR within each of BMI tertile made by analysis of variance, adjusted for age and maturation stage at ages 9 to 10 years. L indicates low; M, middle; U, upper.

Table 3
Significant explanatory variables for metabolic syndrome *z* score at ages 18 to 19 years, by stepwise regression, from candidate explanatory variables: initial visit age, maturation stage, and 9 BMI*HOMA-IR interaction tertile groups

Significant explanatory variable	β	SE (β)	Partial R^2	P
Ages 9-10 y BMI upper tertile and IR upper tertile	+2.49	0.33	12.0%	<.0001
Ages 9-10 y BMI lower tertile and IR lower tertile	−1.17	0.34	3.0%	<.0001
Ages 9-10 y BMI upper tertile and IR middle tertile	1.18	0.43	1.4%	.0059

(yes/no) [18] as the dependent variable, and age, race, and indicators of ages 9 to 10 years 9 BMI*HOMA-IR interaction groups as explanatory variables.

Stepwise regression was also carried out with the metabolic syndrome *z* scores at ages 18 to 19 years as the dependent variable and the following explanatory variables at ages 9 to 10 years: age, maturation stage, and 9 BMI*HOMA-IR interaction groups (Table 3).

3. Results

The analysis sample for this report consisted of 475 girls (194 white, 281 black) with the complete data needed for analyses (Tables 1 and 2). As displayed in Table 1, at ages 9 to 10 years, black girls had higher BMI, insulin, HOMA-IR, and waist circumference than white girls. As displayed in Table 2, at ages 18 to 19 years, black girls had higher BMI, waist circumference, insulin, glucose, HOMA-IR, HDL-C, and systolic blood pressure, and lower triglycerides. However, at ages 18 to 19 years, black girls did not differ from whites by metabolic syndrome *z* score or the percentage with metabolic syndrome (Table 2).

Using the glucose of at least 100 mg/dL cut point in definition of the metabolic syndrome, the stepwise logistic regression showed that the aggregated *z* score was a highly significant ($P < .0001$) explanatory variable for metabolic syndrome (percentage of concordant = 99.1%, AUR = 0.991). The likelihood of having the metabolic syndrome rose 2.9-fold for each 1-unit increment in the aggregate *z* score (OR = 2.92; 95% confidence interval [CI], 2.02-4.22).

Using the glucose (of at least 110 mg/dL cut point in definition of the metabolic syndrome, the stepwise logistic regression showed that the aggregated *z* score was a highly significant ($P < .0001$) explanatory variable for metabolic syndrome (percentage of concordant = 98.9%, AUR = 0.989). The likelihood of having the metabolic syndrome rose 2.7-fold for each 1-unit increment in the aggregate *z* score (OR = 2.68; 95% CI, 1.90-3.79).

In Fig. 1, for the total cohort, the mean ± SD of race-specific aggregate *z* scores for 9 BMI*HOMA-IR tertiles was displayed; the lowest summed *z* score was observed for subjects in the lowest tertiles for both HOMA-IR and BMI (−1.15 ± 2.05), and the highest summed *z* score (2.58 ± 3.11) was in subjects in the highest tertiles for both HOMA-IR and BMI ($P < .0001$). Within the lowest BMI tertile, the aggregate *z* score was higher in the middle HOMA-IR tertile than in the lower HOMA-IR tertile (Fig. 1). When BMI was in the upper tertile, there were progressive increments in the summed *z* score as HOMA-IR rose (Fig. 1).

Using the glucose of at least 100 mg/dL cut point in the definition of metabolic syndrome, stepwise logistic regression revealed that, among race, age, and the status of 9 BMI*HOMA-IR interaction groups at ages 9 to 10 years, the only significant predictor for metabolic syndrome at ages 18 to 19 years was being in both top BMI and top HOMA-IR tertiles ($P = .0008$; OR = 4.76; 95% CI, 1.92–11.8).

Using the glucose of at least 110 mg/dL cut point in the definition of the metabolic syndrome, stepwise logistic regression revealed that, among race, age, and the status of 9 BMI*HOMA-IR interaction groups at ages 9 to 10 years, the only significant predictor for metabolic syndrome at ages 18 to 19 years was being in both top BMI and top HOMA-IR tertiles ($P = .004$; OR = 3.71; 95% CI, 1.42–9.70).

As displayed in Table 3, by stepwise regression, with ages 18 to 19 years *z* scores as the dependent variable and age, maturation status, and the 9 BMI*HOMA-IR interaction groups at ages 9 to 10 years as the explanatory variables, the highest tertile BMI*highest tertile HOMA-IR group at ages 9 to 10 years was positively associated with aggregate *z* score (partial $R^2 = 12\%$, $P < .0001$). Conversely, the lowest tertile BMI*lowest HOMA-IR group was inversely associated with the aggregate *z* score and, although significant ($P < .0001$), explained a small amount (3%) of the variation of the metabolic syndrome *z* score at ages 18 to 19 years (Table 3). The highest tertile BMI*middle tertile HOMA-IR group was positively associated with *z* score ($P = .006$), but explained only a small amount (1.4%) of the variation of the metabolic syndrome *z* score (Table 3).

4. Discussion

In adults, IR is probably the major driver of the aggregation of risk factors that comprise the metabolic syndrome [19]. In a study by Weiss et al [8], factor analysis showed a strong loading of IR to an obesity–glucose metabolism factor. Insulin resistance is also an independent risk factor for metabolic syndrome after adjustment for contributions of adiposity [8]. Using data from the National Health and Nutrition Examination Survey, Li and Ford [20] reported (by factor analysis) that waist circumference and fasting insulin were equal major components of the metabolic syndrome in adolescents. In our 10-year prospective study, in agreement with Li and Ford [20] and Weiss et al [8], upper tertile HOMA-IR was closely related to aggregate *z* score for

metabolic syndrome, with a nearly linear relationship as insulin tertiles rose in the top BMI tertile group. Moreover, by stepwise regression, the highest tertile BMI*highest tertile HOMA-IR group at ages 9 to 10 years was positively associated with the aggregate z score (partial $R^2 = 12\%$, $P < .0001$). Conversely, the lowest tertile BMI*lowest tertile HOMA-IR group was inversely associated with the aggregate z score, explaining 3% of the variance of the metabolic syndrome z score at ages 18 to 19 years ($P < .0001$). Our prospective study suggests that being in the lowest tertile BMI*lowest tertile HOMA-IR group at ages 9 to 10 years protects against development of metabolic syndrome at ages 18 to 19 years, whereas being in the highest tertile BMI*highest tertile HOMA-IR group at ages 9 to 10 years promotes development of metabolic syndrome at ages 18 to 19 years. Moreover, the highest BMI*middle tertile HOMA-IR group explained 1.4% of the variance of the metabolic syndrome z score at ages 18 to 19 years ($P = .006$). Our data should, speculatively, facilitate focus on subgroups of 9- to 10-year–old girls in whom primary prevention of metabolic syndrome 10 years later may be feasible.

Our study is also congruent with the report of Cruz et al [4]. Insulin resistance and hyperinsulinemia have effects on cardiovascular disease risk factors in children independent of other known risk factors like BMI and family history. Thus, fasting insulin levels in 6- to 9-year–old children predicted their blood pressure at ages 9 to 15 years [21]; and in 5- to 9-year–old Pima Indian children, fasting insulin was associated with the degree of 9-year weight gain [22]. The Bogalusa Heart Study reported greater waist circumference and higher insulin levels in pediatric offspring of parents with type 2 diabetes mellitus [23], and 8-year data from Bogalusa show a strong association between persistently high fasting insulin levels and the development of cardiovascular disease risk factors in children and young adults [24]. Insulin resistance (from clamp studies) and obesity have independent effects on cardiovascular risk factor levels in children, and risk factor levels are greater than expected in obese children with IR than children with either fatness or IR alone [25]. Although the Bogalusa Heart Study was initiated before Kalkhoff and colleagues [26] identified central adiposity as a predictor of diabetes and other metabolic disorders, Bogalusa investigators have reported that persistent high insulin [27] and overweight, identified by body mass index instead of waist circumference [28], were associated with higher levels of the factors in the metabolic syndrome later in life.

Our study has the following limitations. First, participants were not a random selection of the United States, as in the National Health and Nutrition Examination Survey [29], but came from a biracial schoolgirl population and from a health maintenance organization program. Thus, the data, although suggestive, need to be confirmed and cannot be extrapolated to all adolescent girls. Second, we used fasting glucose and insulin values in the HOMA-IR equation to estimate IR, rather than the more accurate euglycemic clamp [16].

Primary prevention of development of metabolic syndrome in late adolescence and young adulthood might start with approaches to reduce IR and obesity at ages 9 to 10 years. Freemark and Bursey [30] treated 29 obese black and white 12- to 19-year–old adolescents with diet and metformin, successfully reducing both insulin and weight. Given the progressive increase in a summary z score for metabolic syndrome as HOMA-IR rose within girls in the top tertile for BMI, we speculate that metformin has promise in primary prevention of metabolic syndrome if initiated in hyperinsulinemic adolescents.

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