Obesity and the Development of Insulin Resistance and Impaired Fasting Glucose in Black and White Adolescent Girls

A longitudinal study

DAVID J. KLEIN, MD, PHD[1]
LISA ARONSON FRIEDMAN, SCM[2]
WILLIAM R. HARLAN, MD[3]
BRUCE A. BARTON, PHD[2]
GEORGE B. SCHREIBER, DSC[4]
ROBERT M. COHEN, MD[5]
LINDA C. HARLAN, PHD[6]
JOHN A. MORRISON, PHD[7]

OBJECTIVE — Age at onset of type 2 diabetes has decreased during the past 20 years, especially in black women. Studies of factors associated with insulin resistance and hyperglycemia in preadolescent and adolescent populations are essential to understanding diabetes development.

RESEARCH DESIGN AND METHODS — The National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study (NGHS) is a 10-year cohort study of the development of obesity in black and white girls. Two NGHS centers examined the associations of obesity, puberty, and race with fasting insulin, glucose, and homeostasis model assessment of insulin resistance (HOMA-IR; a calculated index of insulin resistance) measures at 9–10 years of age (baseline) and 10 years later.

RESULTS — Black girls had greater baseline and year-10 BMI than white girls, with a greater 10-year incidence of obesity. BMI-insulin correlations were positive in both black and white girls at both visits, but insulin remained higher in black girls after controlling for BMI. In black girls, insulin and HOMA-IR were higher in the prepubertal period (before the emergence of racial differences in BMI), increased more during puberty, and decreased less with its completion. Baseline BMI predicted year-10 glucose and the development of impaired fasting glucose (IFG) in black girls. In white girls, the rate of BMI increase during follow-up predicted these outcomes. The 10-year incidence of diabetes in black girls was 1.4%.

CONCLUSIONS — Black-white differences in insulin resistance are not just a consequence of obesity, but precede the pubertal divergence in BMI. The development of IFG appears to be a function of the rate of increase of BMI in white girls and early obesity in black girls.

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The prevalence of obesity has increased dramatically in children and adults over the past 20 years, and the age at onset of type 2 diabetes has decreased (1,2). The earlier onset may reflect the longer duration of the obese, insulin-resistant state by late adolescence (3). Previous studies demonstrated racial differences in insulin sensitivity in obese preadolescents (4–8). These studies were limited in their ability to explain the development of impaired fasting glucose (IFG) because of their cross-sectional design and small samples.

The National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study (NGHS) is a 10-year cohort study of the development of obesity in black and white girls (9). To explicate the relationships of obesity with insulin resistance and increased glucose in adolescent girls, the centers in Cincinnati, Ohio, and Washington, D.C., measured fasting insulin and glucose levels at baseline (ages 9 and 10 years) and 10 years later. We postulated that racial differences in insulin sensitivity and persistent obesity contribute to the development of higher glucose levels and diabetes in black females.

RESEARCH DESIGN AND METHODS

— The NGHS, conducted under a contract with NHLBI to identify factors associated with the development of obesity in "black" girls, has been previously described (9). The clinical centers enrolled 9- and 10-year-old black and white girls. Race was self-declared as "black" or "white," and enrollment was restricted to racially concordant households. Two clinical centers collected blood for measurement of insulin and glucose in years 1 and 10. The Cincinnati, Ohio, clinic recruited girls from inner-city, urban residential, and suburban public and parochial schools; the Washington, D.C., clinic recruited girls from a health maintenance organization (HMO). Although white girls had higher average socioeconomic status than black girls, there was a wide representation of socioeconomic status in each racial group based on parental education and household income. The institutional review boards of the two centers approved the study, and signed informed consent was

From the [1]Division of Endocrinology and Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; the [2]Maryland Medical Research Institute, Baltimore, Maryland; the [3]National Institute of Mental Health, Bethesda, Maryland; [4]Westat, Rockville, Maryland; the [5]Division of Endocrinology, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio; the [6]National Cancer Institute, Bethesda, Maryland; and the [7]Division of Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

Address correspondence and reprint requests to John A. Morrison, OSB 4, Division of Cardiology, Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229. E-mail: john.morrison@cchmc.org.

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; NGHS, NHLBI Growth and Health Study; NHLBI, National Heart, Lung, and Blood Institute.

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

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obtained from the girls' parents or guardians.

Clinical measures

Obesity was assessed annually according to a standard protocol (9), using the BMI (kg/m^2) as recommended by several expert panels (10–12). The age-sex specific 95th percentile values for BMI from the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts defined obesity at baseline, and a BMI ≥30 kg/m^2 was used at year 10. Trained staff scored pubertal maturation at baseline following modified Tanner standards. Stage 1 was prepubertal. Stage 2 was pubertal (presence of pubic hair and/or areolar development) but premenarchal. Stage 3 was postmenarchal (13).

Insulin and glucose levels were measured after an overnight fast (≥10 h) using the Michigan Diabetes Research and Training Center (Ann Arbor) in year 1 and the Endocrine Lab at the University of Cincinnati/Children's Medical Center in year 10. Both insulin assays used a competitive protein-binding radioimmunoassay. Glucose was measured at baseline using a hexokinase reagent (Boehringer-Mannheim) 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 to11% for insulin and 2 to7% for glucose in year 1 and were 9 and 4%, respectively, in year 10. Homeostasis model assessment of insulin resistance (HOMA-IR) measures, which correlate with estimates of insulin resistance measured by the euglycemic clamp technique, were used as indexes of insulin resistance (14). Following American Diabetes Association recommendations, a fasting glucose ≥110 mg/dl defined IFG and ≥126 mg/dl defined diabetes (15).

Statistical analyses

The associations of insulin with BMI and puberty were examined in cross-sectional analyses at baseline and year 10 and longitudinally in the cohort. Race-specific associations between BMI and insulin concentrations were evaluated using Pearson's correlation coefficients. General linear models were used to test racial differences in insulin levels, adjusting for BMI, age (as a linear term), and pubertal status (at year 1 as a set of indicator variables). We examined differences in the changes in the insulin-glucose relationships from year 1 to 10 using general estimating equations. An intercept (baseline BMI) and BMI slope across visits was calculated for each participant. Logistic regression was used to predict IFG status in year 10 (yes vs. no) with individual baseline BMI and BMI slope as explanatory variables. Because the number of positive cases was small, multiple linear regression was used with the same independent variables to predict glucose levels at year 10. All analyses were performed using SAS version 9.0.

RESULTS

There were 1,491 girls in the two participating NGHS centers at baseline and 1,262 at year 10. There were no significant racial differences in the retention rate (overall 84.6%; 86.4% of black girls and 82.9% of white girls), nor was BMI associated with study dropout. Because the primary focus of NGHS was obesity development, girls could participate in NGHS and not have blood drawn. The analysis cohort for this report included 955 girls having BMI at both baseline and year 10 and fasting glucose at year 10. Differences in baseline BMI between girls included and not included in these analyses were not significant. Differences in year-10 BMI were not significant for black girls, but were for white girls [24.5 (not included) vs. 23.5 kg/m^2 (included), $P = 0.04$]. At baseline, more black girls (339 of 479, 70.8%) were in pubertal stages 2 and 3 than white girls (177 of 484, 36.6%), but few girls in either group were in stage 3.

Black-white differences in obesity and insulin sensitivity at baseline and year 10

Black girls had greater BMI than white girls at ages 9 and 10 years (Table 1). This difference persisted after adjusting for age and pubertal stage. BMI comparisons of prepubertal black and white girls were not significant (stage 1, Table 1). Black girls had a greater prevalence of obesity at baseline (17.6 vs 6.2%) and year 10 (28.8 vs. 11.2%) (both $P < 0.0001$). The 10-year incidence of obesity was 2.5 times greater in black than white girls (13.2 vs. 5.2%).

BMI was significantly and positively correlated with insulin levels in both black and white girls at baseline ($r = 0.44$ and 0.44, respectively, both $P < 0.0001$) and year 10 ($r = 0.48$ and 0.55, respectively, both $P < 0.0001$). Multivariate analyses showed that BMI and race were significant independent predictors of insulin levels at both visits and that pubertal stage was a significant predictor at baseline. The incremental effects of BMI on insulin levels were similar between the races. BMI, race, and, at baseline, pubertal stage explained 26% of the variance in insulin at baseline and 29% at year 10 (both $P < 0.0001$). Race alone explained 7% of the variance at baseline and 5% at year 10.

Black girls had higher mean fasting insulin and HOMA-IR values than white girls at both visits and higher glucose levels at year 10 (Table 1). The baseline differences persisted when analyses were restricted to prepubertal girls, before the divergence in BMI (insulin = 11.5 vs. 8.7, $P = 0.002$; and HOMA-IR = 2.7 vs. 2.1, $P = 0.01$; Table 1). Within ethnic groups, HOMA-IR and fasting insulin values were greater in pubertal than prepubertal girls. The incremental effects of puberty on insulin levels did not differ between races.

Black-white differences in the relationship between fasting insulin and glucose

Fasting insulin values were positively associated with fasting glucose in both racial groups at baseline and year 10 (Fig. 1). The steeper slopes in the regression lines in black girls indicate that they were more insulin resistant than white girls (i.e., more insulin for any given glucose level). The increase in insulin sensitivity that is expected after completion of puberty is reflected in the (lower) slopes seen in year 10 compared with baseline. The magnitude of the decrease was less in black girls (0.60 to 0.50) than in white girls (0.49 to 0.20) ($P < 0.0001$).

Ten-year changes in obesity status and development of IFG

Obesity was more persistent in black than white girls over the 10-year study period: 88.2% of black girls obese at baseline were obese in year 10 compared with 61.2% of white girls. Mean BMI was greater in the girls who were obese at both visits (39.8 and 37.1 kg/m^2 in black and white girls, respectively) than in girls who were obese at year 10, but not baseline (34.6 and 33.5 kg/m^2), making it difficult to separate the effects of obesity duration and magnitude in explaining changes in insulin, HOMA-IR, and glucose levels. Baseline values for these parameters were

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Table 1—*Mean ± SD of age, body composition measurements, fasting plasma insulin (μU/ml), glucose (mg/dl), and HOMA-IR for girls at baseline and year 10, by race and maturation stage*

	Baseline			Year 10		
	Black girls* $n = 500$	White girls* $n = 455$	P	Black girls $n = 500$	White girls $n = 455$	P
Age	10.1 ± 0.5	10.0 ± 0.6	<0.001	19.1 ± 0.6	19.0 ± 0.6	<0.001
BMI (overall)†	19.4 ± 4.2	17.5 ± 3.1	<0.001	27.4 ± 7.6	23.5 ± 5.2	<0.001
Stage 1	17.1 ± 2.6	16.6 ± 2.5				
Stage 2	20.2 ± 4.4	19.0 ± 3.5				
Stage 3	22.3‡ ± 4.4	19.1‡ ± 1.9				
Insulin (overall)†	15.2 ± 10.2	10.1 ± 7.5	<0.001	13.1 ± 10.3	8.8 ± 6.9	<0.001
Stage 1	11.5 ± 7.8	8.7 ± 5.6				
Stage 2	16.3 ± 10.8	12.2 ± 9.2				
Stage 3	21.6‡ ± 8.4	10.6‡ ± 3.1				
Glucose (overall)	93.7 ± 7.3	93.1 ± 6.3	0.24	90.1 ± 24.2	86.3 ± 7.8	0.001
Stage 1	91.4 ± 7.5	92.9 ± 6.4				
Stage 2	94.6 ± 7.0	93.4 ± 6.2				
Stage 3	95.3‡ ± 6.7	91.5 ± 7.8				
HOMA-IR¶ (overall)†	3.6 ± 2.6	2.4 ± 1.9	<0.001	3.0 ± 2.6	1.9 ± 1.6	<0.001
Stage 1	2.7 ± 2.0	2.1 ± 1.4				
Stage 2	3.9 ± 2.7	3.0 ± 2.3				
Stage 3	5.2‡ ± 2.1	2.5‡ ± 0.9				

*There were 138, 335, and 17 black girls and 279, 163, and 2 white girls in pubertal stages 1, 2, and 3, respectively. Statistics by stage do not include 10 black girls and 11 white girls who are missing maturation stage data; †$P < 0.001$ comparison of means between ethnic groups controlling for stage; ‡$P < 0.001$ for comparison of stage within ethnic group; ¶HOMA-IR = 0.056 × [glucose][insulin]/22.5.

each significantly associated with values at year 10. Across all participants, the 10-year changes in BMI were positively correlated with changes in insulin ($r = 0.26$, $P < 0.0001$), HOMA-IR ($r = 0.24$, $P < 0.0001$), and glucose ($r = 0.16$, $P < 0.001$).

There were 15 black and 6 white girls with IFG at year 10. The impact of baseline obesity and the 10-year change in BMI on fasting glucose and the development of IFG were studied using multiple and logistic regression models, respectively. These models gave similar results within race, but identified different predictors in the two ethnic groups. In black girls, baseline BMI, but not the slope of the changes in BMI, predicted year-10 glucose ($P < 0.005$) and IFG status ($P = 0.02$). There was a 12% increase in risk of IFG for every unit increase in baseline BMI (odds ratio [OR] = 1.12, $P = 0.02$). In white girls, it was the rate of BMI increase, not baseline BMI, that predicted year-10 glucose ($P < 0.0001$) and IFG status ($P = 0.002$). In white girls, there was a 7.6-fold increase in risk of IFG for every unit increase per year in BMI (OR = 7.6, $P = 0.002$).

There were seven girls who had glucose values consistent with the diagnosis of diabetes in year 10. All of these girls were black, so the 10-year incidence rate for type 2 diabetes in black girls was 1.4%. Three of these girls were obese at both visits; two of these girls were overweight at baseline and borderline obese (29.7 kg/m^2) or obese at year 10; one was obese at baseline and overweight at year 10 (28.1 kg/m^2); and one was never obese.

CONCLUSIONS — Obesity and other environmental and genetic factors contribute to the evolution of type 2 diabetes through phases of insulin resistance and β-cell failure (16). Particularly alarming are reports that show that the diagnosis of diabetes is occurring at younger ages, especially in black youth (2). Consistent with these findings, there appeared to be seven incident cases of diabetes in black adolescents but none in white girls in this NGHS ancillary study cohort. All but one of the cases were obese, implicating insulin resistance in the pathogenesis. Because obesity and consequent insulin resistance have been shown to have an accelerator effect on progression of both type 1 and type 2 diabetes, and because these diagnoses occur at overlapping ages, it is difficult to predict from our data which diagnosis is most appropriate in the incident cases (17).

The current study documents the evolution of IFG and interrelationships among race, obesity, pubertal development, and insulin resistance. We corroborate reports that show that the incidence of obesity has increased faster in black than in white girls (18) and add that obesity is more likely to be persistent in black girls. Cohort studies like the NGHS can assess the relationships of predictor and outcome variables more precisely than cross-sectional studies because they provide more than one assessment in time, thus controlling for interindividual variation. This is especially important when the variables of interest, like insulin or glucose, may be determined by factors that are themselves changing at variable rates in individuals. Thus, the finding that BMI at ages 9 and 10 in blacks is an important determinant of fasting glucose levels and the risk for IFG 10 years later is especially important. This is in contrast to white girls, in whom the rate of increase in BMI during the 10-year period was more important in predicting these outcomes. These disparate relations between glucose levels and IFG status in year 10 on the one

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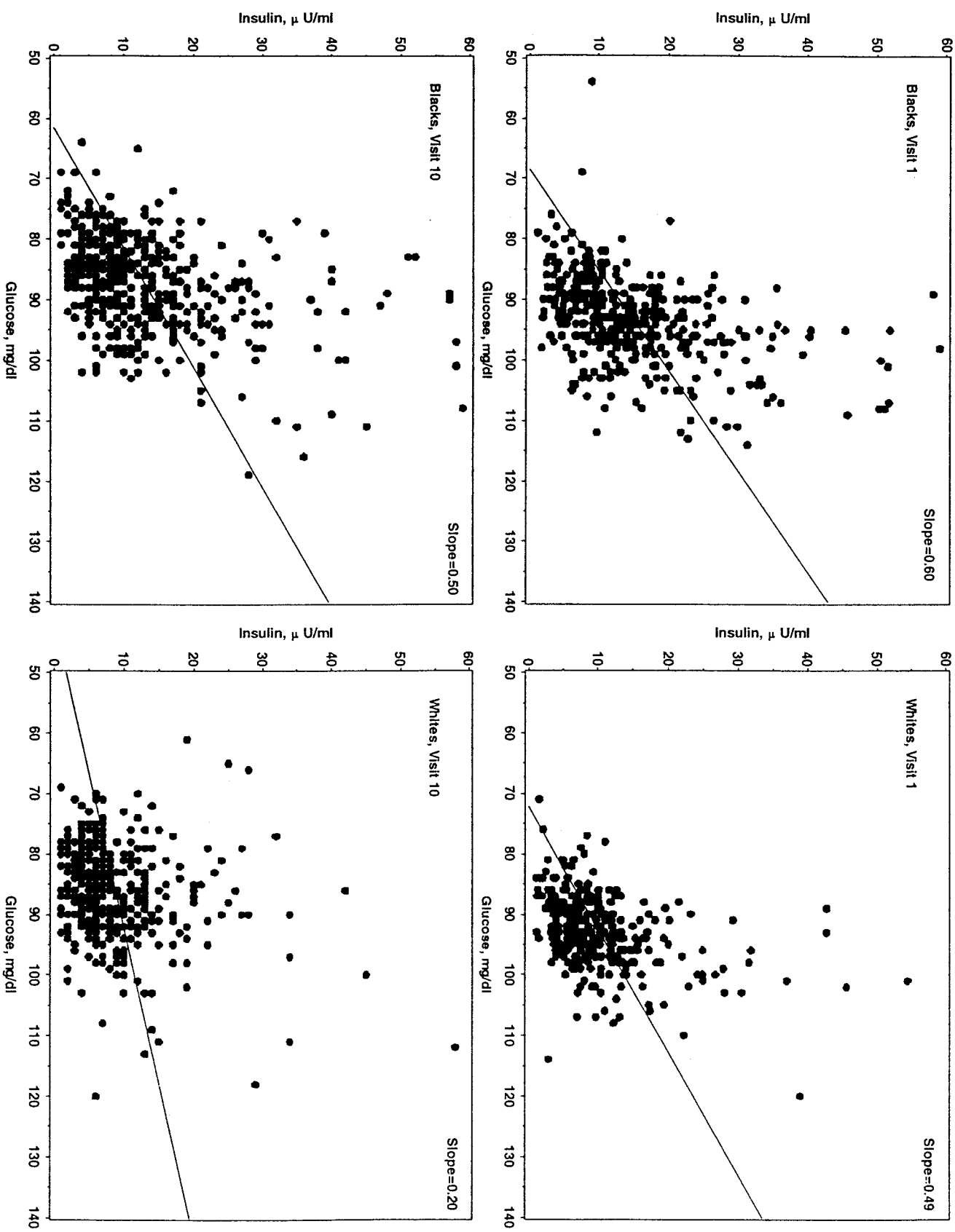

Figure 1—*Insulin and glucose by visit and race.*

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hand and early obesity and the slope of BMI changes on the other are consistent with the marked differences in the percentage of black and white girls who were obese at both baseline and year 10. Previous studies reported increased insulin resistance in prepubertal obese subjects (6–8). The current report extends these findings to indicate that early obesity in black adolescent females is associated with higher fasting blood glucose levels, as well as with increased risk of developing IFG. However, the number of participants who developed IFG was too small to fully test the independent contributions of obesity duration and absolute BMI in the same model.

In both black and white girls, there was a stepped increase in HOMA-IR and fasting insulin levels with pubertal maturation. Increased insulin resistance during puberty and in prepubertal black children has been demonstrated using the euglycemic clamp technique (4,6–8,19–21). The current study, using two separate analyses, confirms that ethnic differences in insulin sensitivity are present before the onset of puberty. First, black-white differences in insulin levels and insulin resistance (HOMA-IR) persisted after controlling for BMI and pubertal stage in the entire cohort. Second, these differences were seen when the analysis was restricted to prepubertal girls, before the emergence of significant black-white differences in BMI. We concur with other studies that show that black girls are more advanced in pubertal development (22) and that the impact of pubertal development and obesity (BMI) on insulin levels do not differ between ethnic groups (8). Importantly, we add to these findings by showing that the magnitude of the postpubertal increase in insulin sensitivity is less in black than white girls.

At both baseline and year 10, fasting insulin levels were positively and independently correlated with fasting glucose values. Racial differences in insulin sensitivity can be inferred from the relationship of fasting insulin to glucose levels (23). That black girls were more insulin resistant than white girls was evident when measured using HOMA-IR as well as when examining the slope of the relationship between insulin and glucose at each visit. Because of the early age at which ethnic differences in insulin sensitivity appear, our findings strengthen the possibility that there are underlying ethnic differences in gene polymorphisms that influence insulin sensitivity or insulin production or metabolism (24–26). Ethnic differences in environmental factors or the interaction of environmental circumstances and gene polymorphisms may also contribute to a group's capacity for physiologic adaptation.

There are several limitations to the current study. First, girls could participate in NGHS without having blood drawn. BMI values were not significantly different in girls who did and did not have blood drawn at baseline or in black girls in year 10, but were lower in white girls who had blood drawn in year 10. Because the associations of BMI with glucose and insulin were positive across the entire cohort and the cohort was large, this difference should not affect analyses of associations between obesity and insulin or glucose, but could have affected the capture of white girls with IFG or overt diabetes. Another limitation to the study is the lack of confirmatory tests in girls having elevated glucose levels. A third limitation is the use of separate labs for insulin and glucose determination in years 1 and 10. No samples were run by both labs, but the labs used similar assays and had good coefficients of variation. The change in labs could have affected the within-race comparisons of year 10 versus year 1, but would not have affected the relative or between-race differences in the changes in slopes. That is, if lab differences explained slope changes, then slope changes would be similar between the races; yet, that is not the case and therefore a race difference is shown. Other major findings of the study—the prepubertal differences in insulin sensitivity and the differences in the roles of baseline BMI and rate of increase in BMI for explaining risk of year-10 IFG—do not depend on direct comparison of baseline and year-10 lab data.

In conclusion, we confirm the presence of intrinsic racial differences in insulin sensitivity, which persist after controlling for obesity (BMI) and pubertal progression. These differences are present before puberty and are magnified by puberty. In addition, the expected increase in insulin sensitivity that occurs with completion of puberty is less in black than white girls. Racial differences in insulin sensitivity influence glucose values and the development of glucose intolerance. Further studies are needed to determine the contributions of obesity duration and magnitude to development of IFG and diabetes in black and white girls.

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