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Preteen insulin levels interact with caloric intake to predict increases in obesity at ages 18 to 19 years: a 10-year prospective study of black and white girls

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Abstract

We evaluated the associations of teenage insulin and adolescent diet with 10-year weight gain in an analysis sample of black and white girls matched for pubertal stage, body mass index (BMI) (or fat mass), and insulin at ages 9 to 10 years. We hypothesized that preteen insulin and insulin resistance would interact with dietary factors to positively predict increases in BMI. Furthermore, we hypothesized that increased insulin and insulin resistance, interacting with higher caloric intake during adolescence, would lead to greater increments in BMI in black girls than in white girls. Prospective 10-year follow-up was performed on 215 pairs of black and white schoolgirls matched at baseline by BMI (or fat mass), insulin, and pubertal stage, with repeated measures of body habitus, insulin, and dietary intake. When matched for BMI, black girls had higher fat-free mass and white girls had higher fat mass at ages 9 to 10 years. Black-white differences in caloric intake were not significant at ages 9 to 10 years, but black girls consumed more calories at age 19 years. Black girls consumed a greater percentage of calories from fat throughout. At age 19 years, black girls had higher BMI, fat mass index, and insulin. When matched at ages 9 to 10 years for fat mass, black girls were heavier, had higher BMI, and had greater fat-free mass. By ages 18 to 19 years, black girls continued to have higher BMI, but had accrued higher fat mass and a higher percentage of body fat. By stepwise multiple regression, 10-year increases in BMI were predicted by ages 9 to 10 years BMI, 10-year change in insulin, and a 3-way interaction between ages 9 to 10 years insulin, adolescent caloric intake, and race (higher in black girls) (all Ps < .0001). Insulin at ages 9 to 10 years interacts with caloric intake to increase BMI by age 19 years. There appear to be intrinsic black-white metabolic differences that lead to greater gains in fat during adolescence in black girls. Evaluating BMI and insulin at ages 9 to 10 years could identify girls (particularly black) who would optimally benefit from dietary and exercise interventions to avoid obesity.

1. Introduction

Black-white differences in the prevalence of obesity in women are thought to contribute significantly to their differences in cardiovascular disease (CVD) morbidity and mortality [1]. Obesity differences begin during the peripubertal and adolescent periods [2]. Evaluating 15-year secular trends in body mass index (BMI) and CVD risk factors in Princeton School District middle-school children (1975-1990), Morrison et al [3] reported that BMI had increased in all sex-race groups, with the largest increase in black females. Concomitantly, the largest increases in total cholesterol, blood pressure, and heart rate were in black females. In the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), increased BMI (>85th percentile) and central adiposity in 9- and 10-year-old black and white girls were associated with increased lipids and blood pressure and with increased clustering of CVD risk factors [4]. Therefore, identifying preteen predictors of adolescent weight gain and central adiposity could provide focused avenues for prevention.

The NGHS was designed to identify factors contributing to black-white differences in weight [5]. The NGHS analyses have been complicated by the fact that black girls were taller and heavier, with greater BMI at enrollment, at ages 9 to 10

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years. These early differences were due in part to the earlier onset of puberty in black girls [5] because onset of puberty increases accretion of height, weight, fat-free mass (FFM), and fat mass (FM). At the same time, however, increased prepubertal body mass is associated with early onset of puberty. The onset of puberty increases systemic insulin resistance (IR) [6] that, in turn, may contribute to increased body weight in childhood and adulthood [7,8].

Two clinical centers of NGHS collected fasting blood for the measurement of insulin in years 1 (ages 9-10 years), 7 (ages 15-16 years), and 10 (ages 18-19 years), in addition to annual measurement of body habitus, pubertal status, and diet [5,9]. In the current report, we evaluate the role of preteen insulin and adolescent diet in 10-year weight gain in 2 analysis samples of paired black and white girls. Because BMI, FM, and insulin all change with pubertal development [6,9], we first matched for pubertal stage, BMI, and insulin at ages 9 to 10 years and, second, matched for pubertal stage, FM, and insulin at ages 9 to 10 years. Thus, the black and white female cohorts started the analysis period with similar measures, by matching. We hypothesized that preteen insulin and IR would interact with dietary factors to positively predict increases in BMI. Furthermore, we hypothesized that increased insulin and IR, interacting with higher caloric intake during adolescence, would lead to greater increments in BMI in black girls than in white girls.

2. Patients and methods

The NGHS was a 10-year multicenter study of the development of obesity and its effects on CVD risk factors in black and white girls [5,9], enrolling 9- and 10-year-old girls. Race was self-declared; and as per the NGHS protocol, enrollment was restricted to racially concordant households. 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 Institutional Review Boards of the 2 Centers, which approved the study. Signed informed consent was obtained from the girls' parents or guardians; and assent, from the girls.

2.1. Clinical measures

Obesity was assessed annually according to a standard protocol [5] using the BMI (kilograms per square meter) [10-12] (Table 1). Beginning in year 2, waist circumference was measured at the minimum waist as an indicator of fat patterning (Table 1). In addition, bioelectrical impedance was measured using a BIA 101 body composition analyzer (RJL Systems, Detroit, MI). Resistance (R) and reactance (Xc) were measured to the nearest ohm on the right side of the body using a tetrapolar placement of electrodes [13]. Measures of R and Xc were used with height and weight to predict FFM, fat-free mass index (FFMI = FFM per square meter), FM, fat mass index (FMI = FM per square meter), and percentage body fat [14].

Self-reported parental BMI data were obtained, along with the schoolgirls' semiquantitative identification of parental obesity by selecting 1 of 9 outline figure rating drawings [15], ranging from very thin to very fat, which best represented their parents' physiognomy. The parental figure ratings score [15] provided by the schoolgirls correlated with both paternal and maternal self-reported BMI ($r = .77$, $P < .0001$; $r = .73$, $P < .0001$).

Pubertal maturation was visually assessed by a modification of Tanner staging to include areolar development instead of breast development [16] by trained, certified staff.

Serum insulin, without stabilizing polyethylene glycol treatment [17], measured by competitive protein-binding radioimmunoassay, and glucose levels were measured after an overnight fast (≥8 hours) using the Michigan Diabetes

Table 1
Median anthropometric and clinical values for 215 black-white girls, pair-matched at enrollment by pubertal stage, BMI, and insulin, at ages 9 to 10 years (visit 1) and ages 18 to 19 years (visit 10)

	At ages 9-10 y (visit 1)				At ages 18-19 y (visit 10)				Changes from visit 1 to visit 10	
	White girls		Black girls		White girls		Black girls		White girls	Black girls
	n	Median	n	Median	n	Median	n	Median	Median % change	Median % change
Age	215	10.0	215	10.1	215	19.0	215	19.1	+90%	+90%
% Pubertal	58.6%				Postpubertal					
Height (cm)	215	140	215	142†	214	165	213	165	+17.5%	+16.1%$^{\parallel}$
Weight (kg)	215	34.9	215	35.5†	214	62.5	215	61.7	+82.5%	+82.8%
BMI (kg/m^2)	215	17.2	215	17.2	214	22.7	213	22.9‡	+32.7%	+37.2%†
Waist (cm)	209	62.0	214	62.0	211	71.8	214	71.4	+18.6%	+17.1%
FFM (kg)	214	25.6	211	27.5$^{\parallel}$	210	44.2	208	44.1	+73.8%	+63.8%$^{\parallel}$
FM (kg)	214	8.8	211	7.0$^{\parallel}$	210	18.1	208	18.8	+115%	+172%$^{\parallel}$
% Body fat	214	26.1	211	20.3$^{\parallel}$	210	29.9	208	30.2	+15.4%	+46.2%$^{\parallel}$
Glucose (mg/dL)	187	93	208	92†	157	86	159	87	−7.1%	−5.2%
Insulin (μU/mL)	215	9.3	215	9.4	165	7.0	161	9.0‡	−24.3%	−7.6%‡
HOMA-IR	187	1.10	208	1.05	155	0.80	157	1.00§	−25.0%	−7.1%†

*$P < .05$, $^{\dagger}P < .025$, $^{\ddagger}P < .01$, $^{\S}P < .001$, and $^{\parallel}P < .0001$: white girls vs black girls compared by Wilcoxon test.

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) (Table 1). 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.

Frozen serum from ages 9 to 10 years, although stored at −80°C, was not kept for remeasurement at ages 18 to 19 years, 9 years later, because of concerns about stability [18] over 9 years of storage. Feldman and Chapman [18] reported decrements in serum insulin of 74% after storage at −20°C for 28 months. Both laboratories used the same competitive protein-binding radioimmunoassay. In statistical analyses where change in insulin was an explanatory variable, we used race-specific z scores in place of raw insulin levels to diminish possible laboratory differences in measurements of insulin (Tables 6-8).

We used fasting insulin as the indicator of IR based on reports by Huang et al [19] and Schwartz et al [20]. Huang et al [19] studied homeostasis model assessment of insulin resistance (HOMA-IR) in white and African American children and concluded that the utility of the HOMA equation in predicting insulin sensitivity was similar to fasting insulin alone. Recently, Schwartz et al [20] compared indices of IR by the euglycemic-hyperinsulinemic clamp and alternative methods, reporting that "surrogate measures are only modestly correlated with the clamp measurements of insulin sensitivity and do not offer any advantage over fasting insulin."

2.2. Dietary data

In 8 of the 10 yearly follow-up visits (years 1, 2, 3, 4, 5, 7, 8, and 10), a 3-day dietary diary was completed by the girls and retrieved by Registered Dietitians. The data were entered and summarized for analyses using the most current version of the Nutrition Data System for Research software developed for the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, for calculation of total calories and of calories from protein, fat, saturated fat, and carbohydrate (Table 2, Fig. 1). The mean (± standard deviation [SD]) number of 3-day diet diary records available in the analysis sample was 6.9 ± 1.3.

2.3. Statistical methods

All analyses were performed using SAS Version 9.1 (SAS, Cary, NC).

Because the radioimmunoassays for insulin for years 1 and 10 were performed in different laboratories, to avoid possible analytical bias, we carried out analyses involving changes in insulin, using the changes in race-specific z scores for these values. The z scores were calculated separately for each race, at enrollment and at year 10, using race-visit–specific means and SDs, as follows: z score = (insulin − mean insulin)/SD.

Studies were done after matching by ages 9 to 10 years pubertal stage, BMI, and insulin (215 pairs, Tables 1, 3-8) and matching by ages 9 to 10 years pubertal stage, insulin, and FM (172 pairs, Table 2).

Wilcoxon nonparametric tests were used to compare differences in study variables between races at baseline (ages 9-10 years) and at follow-up (ages 18-19 years), and percentage of changes, (Tables 1-3). Change in nutrient intake, weight, BMI, waist, FFM, FM, percentage body fat, glucose, insulin, and HOMA-IR were calculated as values at ages 18 to 19 years minus values at ages 9 to 10 years without consideration of fluctuations in the intervening 10 years (Tables 1-3).

Wilcoxon nonparametric tests were used to compare black-white differences in total caloric intake per day throughout the study (Fig. 1).

Separately by race, Spearman correlations between glucose, insulin, or HOMA-IR with measures of BMI,

Table 2
Median anthropometric and clinical values for 172 black-white girls, pair-matched at enrollment by pubertal stage, FM, and insulin, at ages 9 to 10 years (visit 1) and ages 18 to 19 years (visit 10)

	At ages 9-10 y (Visit 1)				At ages 18-19 y (visit 10)				Changes from visit 1 to visit 10	
	White girls		Black girls		White girls		Black girls		White girls	Black girls
	n	Median	n	Median	n	Median	n	Median	Median % change	Median % change
Weight (kg)	172	32.6	172	36.3§	172	59.8	172	64.9‡	+84.7%	+79.7%
BMI (kg/m^2)	172	16.5	171	17.8§	172	22.3	170	24.1§	+33.2%	+35.3%*
Waist (cm)	167	60.5	214	62.3§	170	70.2	171	73.2‡	+18.0%	+16.9%
FFM (kg)	172	24.7	172	27.7‖	172	43.0	172	44.9	+77.2%	+63.1%‡
FM (kg)	172	7.7	172	7.7	172	16.6	172	20.7‡	+119%	+151%‖
% Body fat	172	23.9	172	22.6‡	172	28.9	172	31.8‖	+18.1%	+36.2%‖
Glucose (mg/dL)	143	93	168	92	127	86	139	86	−6.3%	−5.9%
Insulin (μU/mL)	172	9.4	172	9.2	126	7.0	139	9.0‡	−26.8%	+1.0%*
HOMA-IR	143	1.00	168	1.00	121	0.80	136	1.05‡	−27.3%	0.0%

*$P < .05$, †$P < .025$, ‡$P < .01$, §$P < .001$, and ‖$P < .0001$: white girls vs black girls compared by Wilcoxon test.

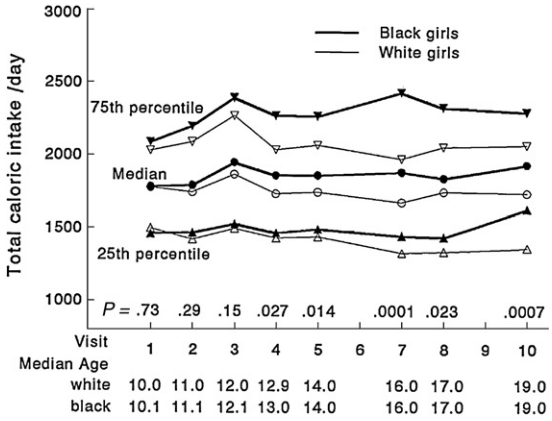

Fig. 1. Median and interquartile range for daily caloric intake in black and white girls from ages 10 through age 19 years. *P* values from Wilcoxon tests.

waist circumference, FFM, FM, and percentage of body weight as fat were calculated for visit 1 (ages 9-10 years) and visit 10 (ages 18-19 years) (Table 4). None of the correlations between insulin or IR with BMI were curvilinear. Spearman correlations were also calculated between BMI, FM, insulin, HOMA-IR, and glucose at ages 9 to 10 years with the same variables at ages 18 to 19 years (Table 5). Spearman correlations were calculated between changes in body mass, insulin, and glucose from ages 9 to 10 years to ages 18 to 19 years (Table 6). Spearman correlations were calculated between parental BMI and parental obesity as judged by their children using figure rating drawings [15].

To explain changes in BMI, after variance-stabilizing transformation (arc tangent transformation), regression analyses were carried out for 215 pairs using a stepwise selection procedure (Table 7). Explanatory variables included race (white = 1, black = 2), age, BMI, insulin, maturation stage at ages 9 to 10 years, and parents' obesity level. Additional explanatory variables included the 10-year change in insulin, mean total calorie intake over 10-year follow-up, and product terms of ages 9 to 10 years insulin with mean total calorie intake, 10-year change in insulin with mean total calorie intake, and race interaction with these 2 terms (Table 7). After arc tangent transformation, similar regressions were done for 10-year change in waist circumference (using waist circumference at ages 10-11 years, the earliest waist measure available, and the last available waist measure) (Table 7). Results were similar whether insulin or HOMA-IR was used in the analyses, so only results based on insulin are presented.

After arc tangent transformation, regression models were also run with the increase in percentage body fat as the dependent variable and age, BMI, insulin, and maturation stage at baseline; parents' obesity level; change in insulin over 10-year follow-up; percentage of calories from protein, from fat, from carbohydrate, and from saturated fat (mean data over 10-year follow-up); and interaction terms (nutrients × baseline insulin, nutrients × change in insulin) as explanatory variables (Table 8). These models were run separately for race (Table 8), after the initial pooled-race model indicated that race was the only significant explanatory variable for increase in percentage of body fat.

3. Results

The 10-year follow-up of NGHS girls included 80% of eligible girls. The 80% of former schoolchildren studied 10 years after their initial assessment did not differ ($P > .05$) from the 20% without follow-up by age, BMI, glucose, or waist circumference. After covariance adjusting for age and race, at ages 9 to 10 years, participants did not differ ($P > .05$) from nonparticipants by fasting serum insulin. Hence, the NGHS cohort did not reflect a selection bias at the time of follow-up. At ages 9 to 10 years (year 1), 518 white and 554 black girls enrolled in the Cincinnati and Washington, DC, clinics had fasting blood drawn for measurement of insulin and glucose concentrations. Although there were more black than white pubertal girls at ages 9 to 10 years (408 of 544 black girls vs 193 of 507 white girls), all black-white comparisons were made after matching by maturation stage, BMI (or FM), and insulin at ages 9 to 10 years (Tables 1 and 2).

Insulin values did not follow normal distributions in either race group.

3.1. Analyses based on BMI matching

The analyses based on matching by ages 9 to 10 years BMI, maturation stage, and insulin were based on 215

Table 3
Median total caloric intake and percentage of calories from protein, fat, carbohydrate, and saturated fat In white and black girls, pair-matched at enrollment by pubertal stage, BMI, and insulin, at ages 9 to 10 years (visit 1) and ages 18 to 19 years (visit 10)

	At ages 9-10 y (visit 1)		At ages 18-19 y (visit 10)		Changes from visit 1 to visit 10	
	White girls (n = 209)	Black girls (n = 178)	White girls (n = 152)	Black girls (n = 178)	White girls (n = 149)	Black girls (n = 148)
	Median	Median	Median	Median	Median % change	Median % change
Total calories	1777	1783	1742	1941[§]	−3%	+7%[‡]
% Protein	14%	14%	14%	14%	−2%	−5%
% Fat	34%	36%*	29%	35%[‖]	−18%	−4%[‖]
% Carbohydrate	53%	52%	58%	52%[‖]	+10%	+4%[§]
% Saturated fat	13%	13%	10%	12%[‖]	−28%	−9%[‖]

*$P < .05$, [†]$P < .025$, [‡]$P < .01$, [§]$P < .001$, and [‖]$P < .0001$: white girls vs black girls compared by Wilcoxon test.

Table 4
Spearman correlations at ages 9 to 10 years (visit 1) and at ages 18 to 19 years (visit 10) between glucose, insulin, and HOMA-IR with measures of BMI, waist circumference, FFM, FM, and percentage of body weight as fat

	BMI		Waist		FFM		FM		% Body weight as fat	
	Black	White	Black	White	Black	White	Black	White	Black	White
Glucose										
Visit 1	.21†	.19*	.22‡	.26‡	.16*	.11	.16*	.16*	.10	.16*
Visit 10	.38§	.14	.38§	.18*	.33§	.16*	.36§	.12	.33§	.07
Insulin										
Visit 1	.45§	.47§	.38§	.43§	.41§	.37§	.33§	.43§	.23‡	.37§
Visit 10	.45§	.46§	.47§	.48§	.36§	.43§	.43§	.44§	.38§	.41§
HOMA-IR										
Visit 1	.47§	.49§	.40§	.46§	.43§	.41§	.34§	.45§	.24‡	.39§
Visit 10	.45§	.45§	.47§	.48§	.35§	.42§	.43§	.43§	.39§	.40§

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .0001$.

matched white-black pairs (Table 1). Of these participants, 165 white girls and 161 black girls had insulin measured at visit 10 (ages 18-19 years, Table 1). As determined by the matching procedure, distributions of BMI did not differ at ages 9 to 10 years (Table 1). Nevertheless, white girls had higher FM (8.8 vs 7.0 kg, $P < .0001$) and percentage body fat (26.1% vs 20.3%, $P < .0001$), whereas black girls had higher median FFM (27.5 vs 25.6 kg, $P < .0001$). At ages 18 to 19 years, black girls had higher BMI (22.9 vs 22.7, $P = .007$) and marginally higher FM (18.8 vs 18.1 kg, $P = .059$).

From median ages 11 to 19 years, black girls had higher BMI (Fig. 2). Black girls also had a higher FFMI (kilograms per square meter) from ages 10 through 19 years (Fig. 3). The FMI (FM in kilograms per square meter) was higher in white girls from ages 10 through 12 years, not significantly different from ages 13 to 18 years, and higher in black girls at age 19 years (Fig. 3). Percentage body fat was higher in white girls from ages 10 to 14 years and not significantly different from ages 15 to 19 years (Fig. 4). Summarizing the changes in body composition from ages 10 to 19 years, black girls had a greater median percentage increase in BMI (37.2% vs 32.7%, $P = .01$), in FM (172% vs 115%, $P < .0001$), and in percentage body fat (46.2% vs 15.4%, $P < .0001$) than white girls (Table 1).

By matching, black and white girls in these analyses did not differ for fasting serum insulin at ages 9 to 10 years; but black girls had higher median insulin at ages 15 to 16 years (11.3 vs 9.7 μU/mL, $P = .001$) and at ages 18 to 19 years (9.0 vs 7.0 μU/mL, $P = .002$) (Table 1). The decrease in insulin accompanying the completion of puberty was less in black than white girls (−7.6% vs −24.3%, $P = .0017$) (Table 1).

Black and white girls consumed a similar number of calories per day (1783 vs 1777 kcal) at ages 9 to 10 years, but black girls consumed more calories at ages 18 to 19 years (1941 vs 1742 kcal, $P = .0005$) (Table 3). Thus, caloric intake decreased 3% in white girls, but increased 7% in black girls (Table 3). In both black and white girls, caloric intake rose with age through age 12 years (Fig. 1). The divergence in caloric intake first occurred at age 13 years and was present at every dietary evaluation thereafter, with white girls ingesting fewer calories over time and black girls ingesting more calories over time (Fig. 1).

Black girls consumed a larger percentage of calories as fat at both ages 9 to 10 years (36% vs 34%, $P = .027$) and

Table 5
Spearman correlations between ages 9 to 10 years BMI, FM, insulin, HOMA-IR, and glucose with ages 18 to 19 years BMI, FM, insulin, HOMA-IR, and glucose

Ages 18-19 y BMI			FM		Insulin		HOMA-IR		Glucose	
	Black	White	Black	White	Black	White	Black	White	Black	White
Ages 9-10 y										
BMI	.71§	.72§	.62§	.64§	.27‡	.29‡	.27‡	.28‡	.26‡	.09
FM	.57§	.64§	.62§	.68§	.24†	.27‡	.24†	.24†	.20†	.07
Insulin	.24‡	.32§	.19†	.25‡	.15	.25‡	.16†	.24†	.18*	.004
HOMA-IR	.25‡	.31§	.21†	.24‡	.15	.23†	.15	.21*	.18*	−.01
Glucose	.24‡	.06	.23†	−.0007	.09	.05	.10	.07	.32§	.16*

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .0001$.

Table 6
Spearman correlations between changes (Δ) of BMI, waist circumference, FFM, FM, percentage of body weight as fat, insulin *z* score, glucose, and HOMA-IR from visit 1 to visit 10

	ΔBMI		ΔWaist		ΔFFM		ΔFM		Δ%Fat		ΔInsulin *z*		ΔGlucose	
	Black	White	Black	White	Black	White	Black	White	Black	White	Black	White	Black	White
ΔWaist	.85§	.81§												
ΔFFM	.73§	.77§	.67§	.67§										
ΔFM	.86§	.94§	.75§	.78§	.52§	.76§								
Δ%Fat	.58§	.56§	.51§	.48§	.11	.18†	.74§	.58§						
ΔInsulin *z*	.28‡	.27†	.30§	.27†	.29‡	.31§	.17*	.23†	.18*	.26‡				
ΔGlucose	.25‡	.17*	.22†	.26†	.23†	.22†	.26‡	.15	.15	.04	.25†	.30‡		
ΔIR	.31§	.33§	.32§	.33§	.29‡	.33§	.18*	.26†	.20*	.29‡	.996§	.996§	.26†	.32‡

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .0001$.

ages 18 to 19 years (35% vs 29%, $P < .0001$) (Table 3). During adolescence, fat consumption decreased in both groups, but decreased more in white than black girls (18% vs 4%, $P < .0001$) (Table 3). Consumption of saturated fats was less in white girls at ages 18 to 19 years (10% vs 12%, $P < .0001$). White girls had marginally higher consumption of carbohydrates at baseline (53% vs 52% $P = .061$) but higher consumption at ages 18 to 19 years (58% vs 52%, $P < .0001$) (Table 3). Thus, the changes in caloric intake and in the pattern of fat, saturated fat, and carbohydrate consumption as a percentage of calories during adolescence differed significantly between black and white girls (Table 3).

At ages 9 to 10 years and 18 to 19 years, glucose and insulin were, for the most part, all significantly correlated with BMI, waist circumference, FFM, FM, and percentage body fat (Table 4). The relationships between insulin and BMI and between insulin and other measures of body mass in Table 4 were linear, not curvilinear.

3.2. Analyses based on FM matching

After matching black and white girls by FM, maturation stage, and insulin at visit 1 (ages 9-10 years), we studied 172 white-black pairs of girls at ages 9 to 10 years and 18 to 19 years (Table 2). Of these 172 pairs, 126 white and 139 black girls had insulin measured at visit 10 (Table 2). After matching for FM, pubertal stage, and insulin, at ages 9 to 10 years, black girls were heavier, had higher BMI, and had greater FFM (Table 2). By ages 18 to 19 years, black girls continued to have higher weight and BMI, had accrued higher FM, and had a higher percentage body fat (Table 2).

3.3. Longitudinal BMI-insulin associations

As summarized in Table 5, BMI at ages 9 to 10 years was closely correlated with BMI and FM at ages 18 to 19 years and was correlated with insulin, HOMA-IR, and glucose (Table 5). Insulin at ages 9 to 10 years was

Table 7
Significant predictors for 10-year change in BMI and waist circumference in black and white girls from ages 9 to 10 years (visit 1) to ages 18 to 19 years (visit 10)

Response variables/significant explanatory variables	*β*	SE (*β*)	Partial R^2	*P*
BMI increase (n = 325)				
Baseline BMI	+0.042	0.0084	8.2%	<.0001
Change in insulin *z* score	+0.19	0.022	11.1%	<.0001
Baseline insulin × total calories × race	+0.0000055	0.0000011	5.8%	<.0001
Waist increase (n = 320)				
Change in insulin *z* score	+0.27	0.034	8.5%	<.0001
Baseline insulin	+0.032	0.0057	8.1%	<.0001

Regression model by stepwise selection from explanatory variables: race (white = 1, black = 2), age, BMI, insulin, and maturation stage at baseline, parents' obesity level, change in insulin *z* score over 10-year follow-up, total calorie intake (mean of interviews) during 10-year follow-up, and interaction terms (total calorie intake × baseline insulin, total calorie intake × change in insulin *z* score, total calorie intake × baseline insulin × race, total calorie intake × change in insulin *z* score × race).

Table 8
Significant predictors for 10-year change in percentage body fat separately in white and black girls between ages 9 to 10 years (visit 1) and ages 18 to 19 years (visit 10)

Response variables/significant explanatory variables	*β*	SE (*β*)	Partial R^2	*P*
Percentage of body fat increase for white girls (n = 162)				
Baseline BMI	−0.016	0.0034	13.5%	<.0001
Change in insulin *z* score × % of total calories as protein	+0.0016	0.00063	4.5%	.012
% of calories as saturated fat	+0.016	0.0061	3.5%	.0094
Father's obesity level	+0.016	0.0079	2.1%	.038
Percentage of body fat increase for black girls (n = 148)				
Change in insulin *z* score × % of total calories as protein	+.0024	.0011	3.6%	.022

Regression model by stepwise selection from explanatory variables: age, BMI, insulin, and maturation stage at baseline, parents' obesity level, change in insulin *z* score over 10-year follow-up, percentage of calories from protein, from fat, from carbohydrate, and from saturated fat (mean of interviews) during 10-year follow-up, and interaction terms (nutrients × baseline insulin, nutrients × change in insulin *z* score).

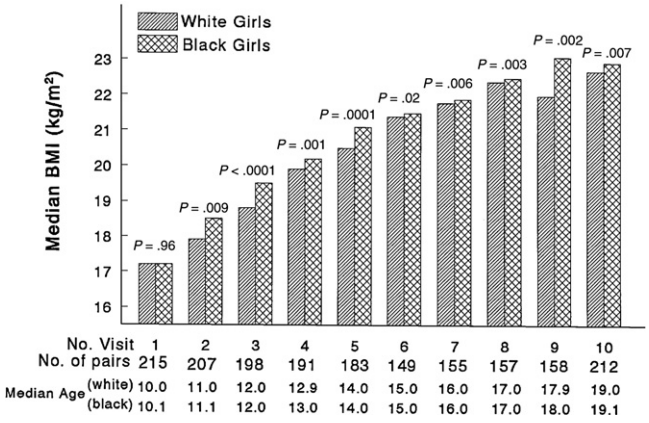

Fig. 2. Median BMI (in kilograms per square meter) at each visit in black vs white girls, ages 10 to 19 years, with black and white girls matched at age 10 years by pubertal status, BMI, and insulin. *P* values from paired Wilcoxon tests.

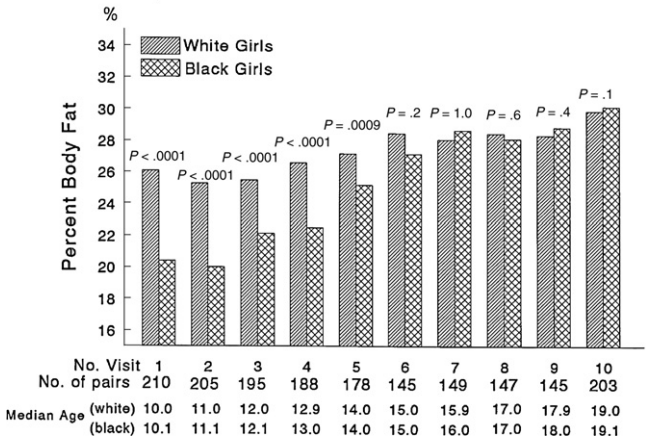

Fig. 4. Median percentage body fat at each visit in black vs white girls, ages 10 to 19 years, with black and white girls matched at age 10 years by pubertal status, BMI, and insulin. *P* values from paired Wilcoxon tests.

positively correlated with BMI and FM at ages 18 to 19 years (Table 5).

Ten-year changes in insulin *z* scores were significantly correlated with 10-year changes in BMI, waist, FFM, FM, and percentage body weight as fat (Table 6).

Ten-year change in BMI was significantly associated with ages 9 to 10 years BMI, with the 10-year change in insulin *z* score, and with a 3-way interaction term of ages 9 to 10 years insulin, average 10-year caloric intake, and race (Table 7). Twenty-five percent of the variance in BMI increase during the 10-year follow-up could be accounted for by change in insulin *z* score, baseline BMI, and the 3-way interaction of age 10 years insulin, total calories over 10 years, and race (Table 7). The interaction of caloric intake during adolescence and ages 9 to 10 years insulin had a greater effect on the increase in BMI in black girls than white girls (Table 7), superimposed on the significantly greater intake of calories by black girls (Table 3, Fig. 1). However, there was no significant threshold effect for BMI; girls with top-quintile BMI at ages 9 to 10 years did not have larger increases in BMI over the 10 years of follow-up than the girls in the lower quintiles (data not shown).

The 10-year increase in waist circumference was associated with the 10-year change in insulin *z* score (partial R^2 = 8.5%, $P < .0001$) and with ages 9 to 10 years insulin (partial R^2 = 8.1%) (Table 7). The regression model explained 16.6% of the variance in waist circumference changes over the 10-year follow-up (Table 7).

In analyzing factors explaining the increase in percentage body fat, in white girls, the change in percentage body fat was associated with ages 9 to 10 years BMI, with the interaction of the change in insulin *z* score with protein as a percentage of calories, with the percentage of calories as saturated fat, and with the paternal anthropometric obesity score [15] (Table 8). These explanatory variables accounted for 23.6% of the variance in the increase in percentage body fat in white girls (Table 8). To explain the negative coefficient associated with ages 9 to 10 years BMI, we examined the mean BMI at years 1 and 10 in girls who were pubertal vs prepubertal at baseline, noting the mean change in BMI in the subgroups. At ages 9 to 10 years, pubertal girls had higher BMI (18.4 vs 16.2 kg/m^2, $P < .0001$) and higher percentage body fat (26.6% vs 24.2%, $P = .003$); but at year 10 (ages 18-19 years), there was no difference in percentage body fat (30.3% vs 28.6%, $P = .14$). Thus, the girls who were pubertal at enrollment had higher baseline BMI and a smaller increase in percentage body fat, whereas girls who were prepubertal at enrollment had more growth yet to come.

In black girls, similar to white girls, the change in percentage body fat was associated with the interaction of the change in insulin *z* score with protein as a percentage of calories (Table 8).

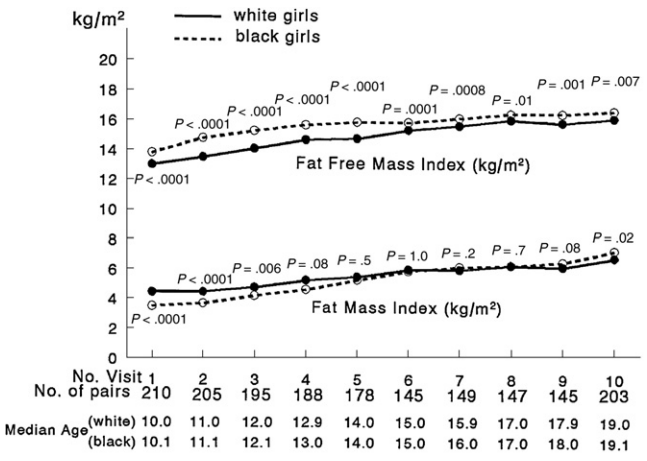

Fig. 3. Median FFMI (in kilograms per square meter) and FMI (in kilograms per square meter) at each visit in black vs white girls, ages 10 to 19 years, with black and white girls matched at age 10 years by pubertal status, BMI, and insulin. *P* values from paired Wilcoxon tests.

4. Discussion

The central, novel findings in our 10-year prospective, longitudinal study of the development of obesity in black and white girls, matched by BMI (or FM), maturation status, and fasting serum insulin at ages 9 to 10 years, were as follows:

1. Higher insulin at ages 9 to 10 years interacted with higher caloric intake to produce a greater increase in BMI, and this effect was greater in black than white girls. We speculate that this insulin × caloric intake × race interaction is central to an intrinsic black-white metabolic difference from ages 9 to 10 years to ages 18 to 19 years in which black girls gain more fat than white girls through adolescence.
2. From the BMI matching data, despite equal BMI at baseline and a lower FM at baseline, black girls had a higher BMI at ages 18 to 19 years than white girls. From the FM matching data, despite equal FM at baseline and a lower percentage body fat, black girls had higher FM and higher percentage body fat at ages 18 to 19 years. This implies that when matched "metabolically" at baseline, black girls gain more FM than white girls through adolescence. Along with the BMI matching data, this finding suggests that there is an intrinsic black-white metabolic difference from ages 9 to 10 years to ages to 18 to 19 years in which black girls gain more fat than white girls through adolescence. Accretion of more FM and higher BMI over a 10-year period are consistent with higher caloric intake at age from ages 13 to 19 years in black girls.
3. At ages 9 to 10 years, black and white girls had different body composition despite their similar (matched) BMI, with black girls taller, heavier, and with greater FFM, and white girls with greater FM and percentage body fat.
4. Black girls had greater 10-year increases in BMI and smaller postpubertal decrements in insulin, and so had significantly greater BMI and insulin at ages 18 to 19 years.
5. Ten-year change in insulin *z* score was a positive predictor of increases in BMI and waist circumference.

These results suggest that reducing insulin levels and moderating caloric intake from ages 9 to 10 years to ages 18 to 19 years should be beneficial for overweight girls with particular relevance in black girls. Because BMI at ages 9 to 10 years was a significant predictor of 10-year increments in BMI, increased BMI at ages 9 to 10 years should alert the clinician to check insulin (and IR) levels and discuss optimal diets and exercise programs, particularly in black girls.

The finding of a positive role for hyperinsulinemia interacting with 10-year caloric intake to increase weight gain is similar to reports by Odeleye et al [7] in Pima Indian children and Mosca et al [8] in adults, but conflicts with reports by Travers et al [21], Maffeis et al [22], and Hoffman et al [23] who found that IR leads to less weight gain and less body fatness. More research is needed to determine why IR appears to have such different effects in these different study populations.

In our current report, congruent with results from previous tracking studies [24-26], preteen BMI was a major, independent predictor of change in BMI at ages 18 to 19 years in girls.

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 [27], but came from a biracial school population and an HMO program. Thus, the data, although suggestive, need to be confirmed and cannot be extrapolated to all adolescent girls. Second, magnetic resonance imaging [28] or computed tomography visceral fat measurements to estimate intra- and extravisceral fat measurements were not done. Third, 3-day dietary diary data may less optimally reflect actual dietary intake than a 7-day record [29]. Fourth, the measurements of insulin levels at ages 9 to 10 years and at ages 18 to 19 years were performed in 2 different laboratories; and although each laboratory used competitive protein-binding radioimmunoassays, this could represent a potential problem because the same insulin assay in different laboratories may give different results [30]. However, in the regression models that included change in insulin, *z* score transformation of insulin or IR provided nearly identical results as the untransformed data. This suggests that the observations of the effects of changes in insulin were independent of putative assay differences. Fifth, we used fasting insulin and glucose values to estimate IR, rather than the more accurate euglycemic clamp [31].

If elevated insulin is documented at ages 9 to 10 years, accompanied by obesity, and if it increases during adolescence, then steps to restrict diet, increase physical activity, and decrease insulin and IR may, speculatively, be warranted. An intensive nutrition program combined with strength training failed to produce changes in insulin sensitivity or body composition in obese Latino adolescents [32]. In obese adolescents in Tennessee, whereas lifestyle changes did not produce significant weight loss, metformin plus lifestyle intervention resulted in significant weight loss [33]. In a randomized, double-blind, placebo-controlled trial in adolescents with IR, diet-exercise modification did not lead to weight loss; but addition of metformin increased weight loss in girls [34]. In Australian obese children, in a randomized, double-blind, crossover trial, metformin therapy resulted in significant improvement in body composition and fasting insulin [35]. In normoglycemic morbidly obese adolescents, a randomized, double-blind, placebo-controlled trial revealed that combined metformin treatment and low-calorie diet had a significant antiobesity effect in hyperinsulinemic obese adolescents compared with low-calorie diet alone [36]. Freemark and Bursey [37] treated 29 obese black and white 12- to 19-year-old adolescents with diet and metformin, successfully reducing both insulin and weight.

Glueck et al [38,39] have reported that the insulin sensitizer metformin, when combined with diet, reduces IR and weight in obese, hyperinsulinemic adolescent girls with polycystic ovary syndrome. Arslanian et al [40] reported that 1700 mg/d metformin treatment in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance was beneficial in improving glucose tolerance and insulin sensitivity, in lowering hyperinsulinemia, and in reducing elevated androgen levels.

We speculate that diet, exercise, and, if needed, metformin have promise in primary prevention of metabolic syndrome if initiated in hyperinsulinemic obese adolescents. We speculate that initiating these interventions in a conservative, stepped fashion might reduce the development of obesity and development of impaired fasting glucose and type 2 diabetes mellitus, leading to an ultimate goal of primary prevention of both progressive obesity and type 2 diabetes mellitus. In our current study, the significant association between the interaction of ages 9 to 10 years elevated insulin and caloric intake for increases in BMI highlights insulin and diet as major modifiable targets in the prevention of or reduction of obesity, particularly in black girls.

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