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Hyperinsulinemia and metabolic syndrome at mean age of 10 years in black and white schoolgirls and development of impaired fasting glucose and type 2 diabetes mellitus by mean age of 24 years

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Abstract

The objective of the study was to evaluate preteen insulin and metabolic syndrome (MS) as independent predictors of impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM) in black and white females by mean age of 24 years. This was a prospective cohort study. There were 8 measures of fasting glucose and insulin from mean age of 10 years through mean age of 24 years, and insulin also at mean age of 25 years. *Childhood MS* was defined by at least 3 abnormal values among waist circumference, triglyceride, high-density lipoprotein cholesterol, blood pressure, and glucose. *Hyperinsulinemia* was defined by insulin greater than or equal to race-specific 75th percentile. Patients with type 1 diabetes mellitus were excluded. The study was held in schools and in an outpatient clinical center. Participants were schoolgirls (260 white, 296 black). There was no intervention. The outcome measures were IFG (fasting glucose of at least 100 to 125 mg/dL) and T2DM (fasting glucose of at least 126 mg/dL). By the age of 24 years, there were 11 cases of T2DM (2%) and 108 cases of IFG (19%). By the age of 24 years, IFG + T2DM was present in 18% of women (73/412) who had normal insulin–no MS at the age of 10 years vs 28% (34/122) of those with high insulin–no MS at the age of 10 years ($P = .014$) and 67% (10/15) of those with high insulin + MS at the age of 10 years ($P < .0001$). By stepwise logistic regression, significant, independent, positive predictors of IFG + T2DM were first insulin measure in childhood, age at last sampling, childhood MS, change in body mass index over 15 years, and, separately, initial glucose of at least 100 mg/dL and average of all insulin quartile ranks over 15 years. The correlation between childhood insulin *z* score and insulin *z* score 15 years later was $r = .30$, $P < .0001$. Insulin and MS at a mean age of 10 years plus change in body mass index over 15 years, and 15-year average insulin rank independently predict IFG + T2DM by mean age of 24 years, suggesting avenues for primary prevention.

1. Introduction

The metabolic syndrome (MS) predicts future type 2 diabetes mellitus (T2DM) in adults [1,2]. Morrison et al [3] reported that childhood MS predicts adult MS and T2DM 25 to 30 years later, consistent with the report of Chen et al [4] that individual factors in MS track from childhood into young adulthood. In addition, the Bogalusa Heart Study reported that persistent high insulin [5] and obesity (body mass index [BMI]) [6] were associated with higher levels of component factors in MS later in life. Nevertheless, central unanswered questions regarding relationships of childhood insulin and MS to young adult impaired fasting glucose (IFG) and T2DM remain, including the following: (1) Do insulin resistance–hyperinsulinemia and MS independently predict IFG and T2DM? (2) Can MS be associated with IFG + T2DM even in the absence of insulin resistance? A third related question is how well does insulin track from childhood to young adulthood. The Cincinnati clinic of the National Growth and Health Study (NGHS) [7] and its extended follow-up study was able to address these issues in black and white females because of its 15-year follow-up

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extending from mean age of 10 years (age 10) with serial measurements of insulin and glucose to mean age of 24 years (age 24), and insulin also to mean age of 25 years (age 25). In the current report, we addressed whether age 10 insulin and MS independently predict IFG and T2DM 14 years later, and whether insulin tracks for 15 years.

2. Materials and methods

2.1. Informed consent

In the NGHS and the NGHS extension study, procedures followed were in accordance with the ethical standards of the institutional review boards of the centers who approved the study. Signed informed consent was obtained from the girls' parents or guardians, and assent from the girls as minors as well as their signed consent as adults.

2.2. NGHS study

National Growth and Health Study was a 10-year, multicenter cohort study to explicate origins of black-white disparities in obesity and its effects on cardiovascular disease risk factors in women [8]. Race was self-declared; and 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 9- to 10-year-old girls from public and parochial schools in the inner city, within-city residential neighborhoods, and suburban areas. Height, weight, and blood pressure were measured annually by trained staff following standard protocols as previously described [8]. Complete lipid profiles were measured on fasting blood as previously described. In an ancillary project, the Cincinnati clinic measured fasting insulin and glucose in years 1, 7, and 10 (mean ages of 10, 16, and 19). After completion of NGHS, the Cincinnati clinic carried out investigator-initiated studies with yearly measurement of insulin and glucose at mean ages 19 through 24 (insulin, glucose) and mean age 25 (insulin only). There were 8 measures of glucose from mean age 10 through mean age 24, and 9 measures of insulin from mean age 10 through mean age 25.

The NGHS used BMI to assess overweight [8] as recommended by several expert panels [9-11] and waist circumference beginning in year 2 as an indicator of fat patterning.

Fasting glucose was measured at year 1 (mean age 10) using a hexokinase reagent (Boehringer-Mannheim, Federal Republic of Germany) and at years 10 (mean age 19) through 15 (mean age 24) using the glucose oxidase method with the Hitachi 704 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Coefficients of variation ranged from 2% to 7% for glucose.

Insulin levels were measured after an overnight fast (≥8 hours) using the Michigan Diabetes Research and Training Center (Ann Arbor) in year 1 (mean age 10) and the Endocrine Laboratory at the University of Cincinnati/ Children's Medical Center in years 7 (mean age 16), 10 (mean age 19), and years 11 to 16 (mean age 20-25). Serum insulin, without stabilizing polyethylene glycol treatment [12], was measured by competitive protein-binding radioimmunoassay. Coefficients of variation for insulin measurement at mean ages 10, 16, and 19 ranged from 5% to 11%. Frozen serum from age 10, although stored at −80°C, was not kept for remeasurement at ages 19 to 25, 15 years later, because of concerns about stability [13] over up to 15 years of storage. Feldman and Chapman [13] reported decrements in serum insulin of 74% after storage at −20°C for 28 months. Because insulin assays were done in 2 different laboratories, in analyses that incorporated comparing insulin levels over time, insulin levels were transformed into z scores. We used fasting insulin as the measure of insulin resistance. Although the homeostasis model assessment of insulin resistance (HOMA-IR) has been advocated as a measure of IR because it correlates with estimates of IR measured by the euglycemic clamp technique, Huang et al [14] compared estimates of insulin resistance from HOMA-IR to results from a frequently sampled oral glucose tolerance test and concluded that "… a modified HOMA equation accurately predicted insulin sensitivity, but its utility is similar to fasting insulin alone." Outcomes of analyses using HOMA-IR were virtually the same as for insulin (data not shown). Only data for insulin were displayed.

2.3. Diagnosis of diabetes

The NGHS schoolchild subjects having type 1 DM at any time from mean age 10 through mean age 25 were excluded from this report. Diagnosis of diabetes was based on World Health Organization criteria, fasting glucose greater than or equal to 126 mg/dL, and/or self-reported diabetes with treatment by a physician [15]. In the NGHS follow-up (ages 20-25), subjects were asked, "do you have a health condition, if yes, what is it, and do you regularly see a doctor for it?" For subjects responding yes to any of these 3 questions, they were then asked, "do you take any pills or insulin?" With exclusion of girls with type 1 DM, we characterized follow-up diabetes as T2DM. No girls had T2DM at mean age 10. We defined impaired fasting glucose (IFG) as glucose of at least 100 but less than 126 mg/dL to comport with the American Diabetes Association's 2004 definition of IFG [16]. To increase the number of cases for analysis, we combined IFG and T2DM cases in analyses.

Maternal and paternal DM was diagnosed in the NGHS by fasting blood glucose of at least 126 mg/dL and by history of diabetes treated by a physician. At the NGHS girls' mean age 19, parental history of DM was updated.

At follow-up at ages 19 to 24 in the NGHS, we did not have measurement of C-peptides as well as diabetes autoantibody levels, criterion standard methods [17] to distinguish type 1 from type 2 DM.

Table 1
Two models predicting IFG + T2DM by mean age 24 in 556 NGHS black and white females by stepwise logistic regression

Model 1 (n = 556)				
Significant explanatory variables	OR	95% CI	*P*	AUR
Change in BMI	1.14	1.09-1.18	<.0001	0.773
Insulin (μU/mL, earliest measure, age 10 or 16)	1.02	1.01-1.04	.0051	
Age (y, at last sampling)	1.38	1.11-1.72	.0042	
MS at age 10 ± 0.5 y (yes, no)	3.19	1.17-8.70	.024	
Model 2 (n = 545)				
Significant explanatory variables	OR	95% CI	*P*	AUR
Change in BMI	1.11	1.06-1.16	<.0001	0.793
Initial glucose ≥100 mg/dL (yes = 1, no = 0)	4.11	2.09-8.11	<.0001	
Mean of all insulin quartile ranks (4 ascending categories)	1.53	1.16-2.03	.0028	
Age (y, at last sampling)	1.40	1.12-1.77	.0038	

In each model, the *dependent variable* was (IFG & T2DM) vs glucose <100 mg/dL. *The explanatory variables in both models 1 and 2* included race (W = 1, B = 2), 1st BMI, change in BMI (from 1st to last measure), 1st ratio of waist to height, change in ratio of waist to height (from 1st to last measure), pediatric MS, parents' T2DM history, age at last sampling, 1st insulin measure (both continuous and pooled-race quartile category), interaction of 1st insulin measure with race, and change in insulin quartile ranks from 1st measure to last follow-up (up = 1, down = −1, not change = 0).
CI indicates confidence interval; AUR, area under receiver operating characteristic curve.
In model 2, the 5 individual components of the MS, scored abnormal vs normal, and the mean of the insulin quartile ranks during follow-up were added to the explanatory variables used in model 1.

2.4. Diagnosis of MS and hyperinsulinemia at age 10

Metabolic syndrome was defined by at least 3 abnormal values among 5 measures: waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), systolic or diastolic blood pressure, and fasting glucose. Pediatric standards were used to define abnormal levels of triglycerides, waist, and blood pressure because pediatric distributions of these factors differ markedly from adults [18]. Thus, triglycerides of at least 110 mg/dL were defined as elevated, and waist circumference of at least the race-/age-specific 85th percentile was defined as high. Systolic or diastolic blood pressure of at least the age- and height-specific 90th percentile [11,19] was defined as elevated; HDL-C not exceeding 50 mg/dL was defined as low [18]. Glucose of at least 100 mg/dL was defined as elevated to comport with the American Diabetes Association revised definition for IFG guidelines [16]. Hyperinsulinemia was defined by insulin *z* score in the top quartile of the race specific distribution.

2.5. Statistical analysis

All analyses were performed using SAS (Cary, NC) Version 9.1. The first available insulin measure by mean age 16 was used (413 subjects had insulin tested at mean age 10, and 143 additional girls had the first insulin measure at mean age 16). The maximum fasting glucose at ages 19 to 24 was used to define IFG + T2DM.

In Tables 1 and 2, insulin values from black and white girls were pooled together, transformed to *z* scores, then ranked in quartiles. Distributions of race (black, white) in 4 insulin *z* score quartiles were assessed using Mantel-Haenszel χ^2 analyses. Subsequently, race-specific *z* scores for insulin were used and ranked separately by race in quartiles (Tables 3-4, Figs. 1-3). Analyses using pooled (non–race-specific) *z* scores in Tables 3 and 4 and Figs. 1 to 3 provided very similar results to those using race-specific *z* scores (data not shown).

Stepwise logistic regression analysis was used to assess associations of childhood variables with IFG + T2DM by age

Table 2
Relative risk for development of IFG + T2DM by age 24 in 556 NGHS girls

Risk factors for IFG + T2DM	n	IFG + T2DM	Not	RR (95% CI)
Change in BMI in top quartile	139	60 (43%)	79	
Not	417	59 (14%)	358	3.05 (2.25, 4.13)
1st insulin in top quartile	139	50 (36%)	89	
Not	417	69 (17%)	348	2.17 (1.60, 2.96)
Average of all insulin quartile ranks in top quartile	137	59 (43%)	78	
Not	419	60 (14%)	359	3.01 (2.22, 4.07)
MS at age 10	22	12 (55%)	10	
Not	534	107 (20%)	427	2.72 (1.79, 4.13)
Glucose ≥100 at age 10	62	27 (44%)	35	
Not	336	55 (16%)	281	2.66 (1.83, 3.86)

Table 3
Pearson simple correlations between race-specific 1st insulin *z* score (mean age 10 or 16) with later insulin *z* scores during a 15-year follow-up period.

Mean ± SD age		19.1 ± 0.6	20.7 ± 0.8	21.8 ± 0.8	22.9 ± 0.8	23.9 ± 0.8	24.9 ± 0.8
n		396	500	468	455	358	454
Correlations of insulin measures							
White race	*R*	0.53	0.62	0.61	0.25	0.38	0.49
	P	<.0001	<.0001	<.0001	.0004	<.0001	<.0001
Black race	*R*	0.30	0.28	0.14	0.16	0.16	0.16
	P	<.0001	<.0001	.030	.014	.026	.011

24 (Table 1). The dependent variable was IFG + T2DM by mean age 24; and candidate explanatory variables included race (W = 1, B = 2), childhood MS (yes = 1, no = 0), BMI at age 10, 15-year change in BMI, ratio of waist to height at age 11, 15-year change in ratio of waist to height, first insulin measure (both continuous and categorical level—race pooled top quartile as high, bottom 3 quartiles as normal), a race by insulin interaction term, change in insulin quartile ranks from the first measure to the last available measure (up = 1, down = −1, no change = 0), parents' DM history (yes = 1, no = 0), and age at last sampling (top panel, Table 1). In the second model, the 5 component measures of childhood MS and the average insulin quartile ranks over 15-year follow-up were added to the first model explanatory variable list (bottom panel, Table 1). The averaged insulin rank was categorized in 4 ascending quartile levels (Table 1).

In multivariate logistic regression (Table 1), the logistic regression estimate odds ratio (OR) was calculated for any 1-unit change of each explanatory variable, under the assumption that log odds is a linear function of the explanatory variables (multivariate analysis). The OR of one variable is adjusted for the other variables in the same model. The relative risk (RR) in Table 2 was calculated under the assumption that the observed response (IFG + T2DM by age 24) is related with only one explanatory variable at a time in bivariate analysis, not adjusted for other possible explanatory variables.

Estimates of RR for IFG + T2DM by age 24 were calculated for 15-year change in BMI, first childhood insulin in the top quartile, MS at age 10, glucose of at least 100 at age 10, and average of all insulin quartile ranks over 15 years (Table 2).

Subjects were categorized into 4 groups based on their MS status at age 10 and first insulin value (Fig. 1), as follows:

1. Insulin "normal" (<race-specific top quartile) and no MS;
2. Insulin high (race-specific top quartile) and no MS;
3. Insulin normal and MS present;
4. Insulin high and MS present.

The incidence of IFG + T2DM by mean age 24 in these 4 categorical groups was compared by χ^2 test or Fisher exact test (Fig. 1).

In the category group insulin normal–no MS at age 10 (column 1, Fig. 1), the percentage of high insulins (in the race-specific top quartile) at subsequent visits over 15 years was compared in the 73 girls who later developed IFG + T2DM and in the 339 who did not (*P* values from χ^2 test, Fig. 2).

We compared the incidence of IFG + T2DM by mean age 24 in 169 subjects whose first and last insulin *z* score remained in the same quartile using χ^2 and Mantel-Haenszel χ^2 tests (Fig. 3). The χ^2 test was used to compare the incidence of IFG + T2DM between 2 insulin quartile groups, as in 2 by 2 contingency tables. The Mantel-Haenszel analysis was used to assess incidence of IFG + T2DM in 2 by 4 contingency tables, taking advantage of the ordinal nature of the columns.

To evaluate the degree of insulin tracking over time, Pearson correlations of the first insulin *z* score with each subsequent insulin *z* score from age 19 through 25 were calculated (Table 3). As an additional approach to assess tracking of insulin over time, risk ratios for subjects with their first insulin *z* score in the top quartile (vs in the bottom 3 quartiles) to be in the top quartile at each subsequent visit, from age 19 through age 25, were calculated (Table 4).

3. Results

The analysis sample included 556 girls in NGHS, 260 white and 296 black.

When pooled-race insulin quartile ranks were calculated, white girls were disproportionately clustered in the cohort's lowest insulin quartile; and black girls were in the highest insulin quartile ($P < .0001$ for ages 10, 21, 23, 24, and 25). At

Table 4
Relative risk and 95% CI of insulin *z* score being in the highest race-specific quartile (vs in the bottom 3 quartiles) at each subsequent follow-up, for girls whose 1st insulin *z* score in the top race-specific quartile vs in bottom 3 quartiles

	Mean ± SD age	19.1 ± 0.6	20.7 ± 0.8	21.8 ± 0.8	22.9 ± 0.8	23.9 ± 0.8	24.9 ± 0.8
	n	400	504	473	459	362	458
White race	RR, 95% CI	2.13, 1.37-3.31	1.80, 1.16-2.80	1.87, 1.19-2.95	2.43, 1.55-3.82	2.48, 1.51-4.06	1.89, 1.18-3.00
Black race	RR, 95% CI	1.94, 1.20-3.15	1.75, 1.16-2.62	1.92, 1.26-2.91	1.82, 1.19-2.79	1.60, 0.98-2.61	1.96, 1.28-2.98

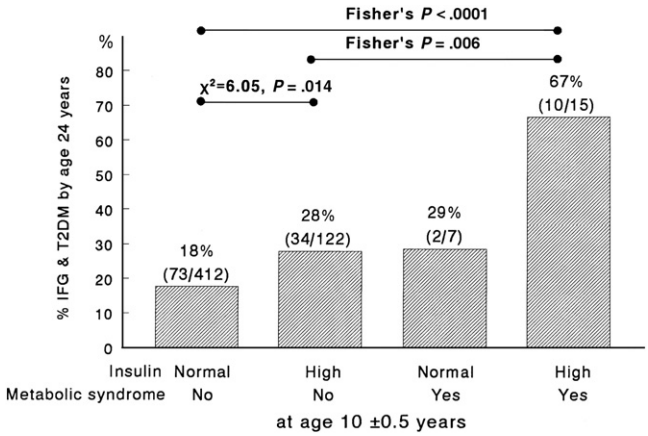

Fig. 1. Prevalence of IFG + T2DM by age 24 by MS and insulin status at age 10. Five hundred fifty-six NGHS schoolgirls characterized by age 10 ± 0.5 years top quartile insulin *z* score (high), bottom 3 quartiles insulin (normal), and MS present or not present. Percentage of schoolgirls in insulin-MS category groups (normal–no MS, high–no MS, normal–yes MS, high–yes MS) with IFG + T2DM by age 24.

age 25, 38% of white and 14% of black girls fell in the lowest group insulin quartile; and 15% of white and 33% of black girls fell in the highest group insulin quartile.

The prevalence of MS at mean age 10 was 4.0% (22/556 girls, Fig. 1). Of the 22 schoolchildren identified with MS at age 10 (columns 3 plus 4, Fig. 1), 15 (68%) had top quartile insulin levels (Fig. 1).

By age 24, there were 11 (2%; 2 W, 9 B) incident cases of T2DM, 108 (19%; 39 W, 69 B) incident cases of IFG, and 437 (79%; 219 W, 218 B) noncases. More cases of IFG + T2DM were observed in black than in white girls (26% vs 16%, $P = .0024$). By age 24 ± 0.8, IFG + T2DM was present in 73 (18%) of 412 women with normal insulin and no MS at age 10, 34 (28%) of 122 women with hyperinsulinemia but no MS at age 10 ($P = .014$), and 10 (67%) of 15 women with hyperinsulinemia plus MS at age 10 ($P < .0001$, Fig. 1). Only 7 women had normal insulin but MS at age 10, and 2 (29%) of these women developed IFG + T2DM by age 24 ± 0.8 (Fig. 1). The 2 women who developed IFG + T2DM never had high insulin concentrations over 15 years of follow-up. Since MS is rare in the absence of hyperinsulinemia in childhood (7/556 girls [1.3%], Fig. 1), the estimate of IFG + T2DM is unstable and lacked power for comparisons to the other 3 categories (Fig. 1).

Of the 412 girls with normal first insulin and no childhood MS, 73 (18%) developed IFG + T2DM by age 24; and 339 (82%) did not (Fig. 1, column 1). The 73 girls who developed IFG + T2DM were much more likely to develop hyperinsulinemia than the 339 girls who did not develop IFG + T2DM at each follow-up (Fig. 2). During the whole 15-year follow-up, 52 (71%) of the 73 girls who developed IFG + T2DM had at least 1 hyperinsulinemia, compared with 145 (43%) of 339 girls free of IFG + T2DM ($P < .0001$).

Independent, significant, positive predictors of IFG + T2DM by age 24 included the 15-year change in BMI, first insulin measure in childhood, age at last sampling, and childhood MS (top panel, Table 1). When values of the 5 MS components plus the mean of all insulin quartile ranks over 15-year follow-up were added as explanatory variables, childhood glucose of at least 100 mg/dL, 15-year change in BMI, age at last sampling, and average of all insulin quartile ranks during follow-up were significant positive explanatory variables (bottom panel, Table 1).

When 15-year change in BMI, childhood insulin, or average of 15-year insulin ranks was in the top quartile, vs the other 3 quartiles, RR of developing IFG + T2DM by age 24 was 3.05, 2.17, or 3.01, respectively (Table 2). When MS

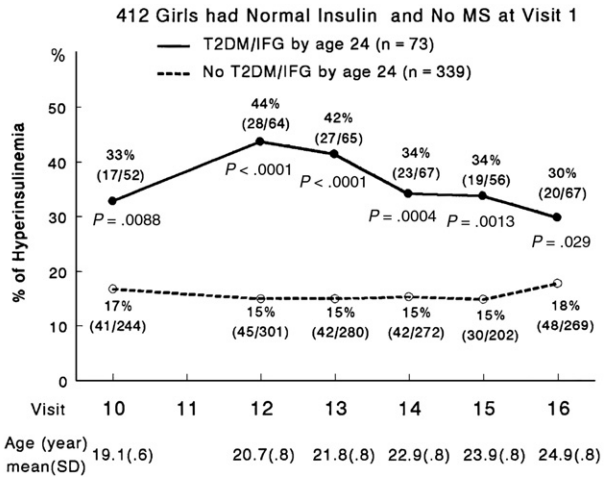

Fig. 2. Prevalence of hyperinsulinemia at visits 10 to 16 in 412 NGHS girls having insulin at age 10 ± 0.5 years in the bottom 3 quartiles insulin and no MS. Percentage of girls having top quartile insulin during follow-up from age 19 to 25, with comparison (by χ^2 analyses) between 73 girls who developed IFG + T2DM by age 24 and 339 who did not.

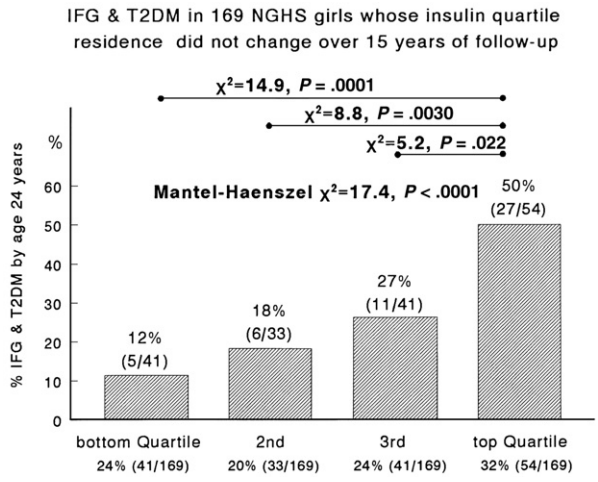

Fig. 3. One hundred sixty-nine NGHS girls whose insulin quartile residence did not change over 15 years of follow-up, 24% remaining in the bottom quartile, 20% in the second quartile, 24% in the third quartile, and 32% in the top quartile. Percentage, by quartile residence, developing IFG + T2DM by age 24. Comparisons by Mantel-Haenszel χ^2 and χ^2 analyses.

was present at age 10 or glucose was at least 100 mg/dL at age 10, then RRs for development of IFG + T2DM by age 24 were 2.72 and 2.66, respectively (Table 2).

In both white and black girls, *z* scores for childhood insulin levels were significantly correlated with follow-up insulin *z* scores (Table 3).

In both white and black girls, if first measured childhood insulin *z* score was in the top race-specific quartile, then over 15-year follow-up, the risk of their insulin *z* scores being in the top race-specific quartile was higher than that of girls with first insulin measure in bottom 3 quartiles (RR > 1, $P < .05$, Table 4).

Residence in the same insulin quartiles over the 15-year follow-up period is displayed in Fig. 3. The percentage of young women with IFG + T2DM by age 24 rose in a stepwise fashion with persistent insulin quartile residence (Mantel-Haenszel $\chi^2 = 17.4$, $P < .0001$, Fig. 3).

4. Discussion

The rising frequency of obesity over the past decade [20] has resulted in increased central adiposity and hyperinsulinemia–insulin resistance, IFG, and T2DM in late adolescence [7].

In the current study, the prevalence of MS was 4.0% at age 10, similar to the finding of Cook et al [18], but higher than that reported by Ford et al [21] using the National Health and Nutrition Examination Survey (NHANES) III data from 10 years earlier. This suggests that the population's increase in obesity has continued unabated [22], amplifying the prevalence of MS. Of the 22 schoolchildren identified with MS at age 10, 15 (68%) had top quartile insulin levels. Impaired fasting glucose and T2DM were most likely to be present (67%) 14 years later in subjects who had both top quartile insulin and MS at age 10.

In the current study, using total cohort (race-pooled) rank of insulin, white girls were clustered in the lowest insulin quartile, whereas black girls were clustered in the top quartile, a finding similar to that of Hannon et al [23]. Lee et al [24] reported that absolute HOMA-IR levels were higher in black than white adolescents; but after adjusting for BMI, there were no black-white differences in HOMA-IR. Weight status was by far the most important determinant of insulin resistance in the study by Lee et al [24], accounting for 29.1% of the variance in HOMA-IR.

In multivariate analyses, childhood insulin and childhood MS independently predicted IFG + T2DM 14 years later in young adulthood in the biracial NGHS schoolgirl cohort. These data are consistent with our report that schoolchildren from the Princeton Follow-up Study with pediatric MS were more likely than their peers to have T2DM 25 to 30 years later as adults [3]. Our findings are also congruent with those of Mattsson et al [25] who carried out a prospective cohort study including 2195 subjects, aged 3 to 18 years in 1980, who were reexamined in 1983, 1986, and 2001. The multivariable logistic regression model selected obesity, male sex, high triglycerides, high insulin, high C-reactive protein, family history of hypertension, and T2DM as significant, positive, independent predictors of adult MS. Youth obesity (BMI >80th age- and sex-specific percentile) was the strongest risk factor for MS. Mattson et al [25] concluded that "… these risk factors at an early stage could help identifying children and adolescence at greater risk of developing MS later in life."

In the current study, the failure of age 10 MS to enter the model when the individual components of the MS were added to the model, particularly childhood glucose of at least 100 mg/dL, suggests that the glucose component of early MS contributes strongly to later development of IFG + T2DM [3,7,26]. The fact that introducing glucose of at least 100 mg/dL as an independent predictor eliminated age 10 MS from the model suggests that elevated glucose at age 10 may identify individuals susceptible to IFG + T2DM. Similarly, Franks et al [27] reported that 3 components of the MS (fasting glucose, HDL-C, and BMI) were independent adult T2DM predictors in 5- to 19-year-old initially nondiabetic American Indians.

When 15-year change in BMI was in the top quartile, childhood insulin was in the top quartile, or the 15-year average of insulin quartile ranks was in the top quartile, the risk of having IFG + T2DM by age 24 was 3.05, 2.17, or 3.01 times higher than being in the bottom 3 quartiles for these variables, respectively. If MS was present at age 10 or glucose was at least 100 mg/dL at age 10, then the RR of having IFG + T2DM by age 24 was 2.72 and 2.66. These increased RRs for IFG + T2DM by age 24 should suggest preventive measures in childhood to deal with progressive obesity, progressive hyperinsulinemia, and MS, not only to ameliorate these cardiovascular disease risk factors, but to facilitate primary prevention of IFG and T2DM.

The association of childhood insulin and average insulin quartile rank over 15 years with presence of IFG + T2DM by age 24 is congruent with the report by Huan et al [28], where insulin resistance determined by the clamp technique was associated with worsening glucose metabolism and diabetes in an 8-year study of African American teenagers. In obese Turkish children [29], indices of insulin resistance correlated with the degree of abnormal glucose tolerance. In Pima Indian children [30], fasting insulin was a significant predictor of diabetes, but did not add to the predictive value above relative weight. Our findings are also congruent with those of Li et al [31] in the cross-sectional NHANES study where adolescents with hyperinsulinemia had a 4-fold higher prevalence of IFG, impaired glucose tolerance, and prediabetes than those without. Neither overweight nor number of cardiometabolic risk factors was significantly associated with prediabetes after adjustment for hyperinsulinemia [31]. Hyperinsulinemia was independently associated with prediabetes and may account for the association of overweight and clustering of cardiometabolic risk factors with prediabetes [31].

The independent association of childhood insulin with IFG + T2DM by age 24 in the current study parallels our observations in 18- to 19-year-old NGHS girls [7] where age 10 insulin resistance (and insulin) and rapidly increasing insulin resistance during adolescence identified girls who were at greater risk of IFG and T2DM by age 19. In addition, insulin interacting with total calories and race in a 3-way interaction term identified black girls who were at greater risk due to weight gain [7].

Our study augments data that insulin resistance–hyperinsulinemia is a key factor in development of both T2DM [32] and MS [33]. Although obesity is a major contributor to insulin resistance, it is not the sole cause of insulin resistance. β-Cell failure is also a key component in development of T2DM [34]. The exact etiology of β-cell failure remains unclear [35-37]. Both insulin resistance and β-cell dysfunction are required for development of T2DM [37].

The finding that 15 (68%) of 22 girls with MS had top quartile insulin at mean age 10 supports Reaven's [38] contention that insulin resistance is the driving force underlying MS on a population basis. Nevertheless, MS did increase risk of future IFG + T2DM through the effects of several MS components. Gerich [39] has argued that insulin resistance–hyperinsulinemia is not a necessary or essential component of T2DM; and 29% of our subjects with normal insulin and free of MS at mean age 10 who developed IFG + T2DM by age 24 never had high insulin on follow-up, a finding that could indicate limited β-cell function from an early age, unable to increase insulin in the face of rising glucose.

In the current study, childhood insulin levels were highly correlated with insulin levels at ages 19 to 25. Moreover, the subjects originally in the top quartile of childhood insulin had higher risk of having insulin in the top quartile from age 19 to 25. In the study by Ronnema et al [40] with 6-year follow-up of insulin in 2433 subjects ages 9 to 24, "tracking of insulin was only moderate, especially in females and young boys."

In the current study, the prevalence of T2DM (2%) was slightly lower than the 3% reported by Nguyen et al [41] in the Bogalusa study; but the prevalence of IFG (19%) was higher than that reported by Nguyen et al (4.5%), with both populations at the approximate same age in adulthood [41].

Our study has the following limitations. The number of cases is modest at follow-up, especially T2DM (n = 11); and when stratifying by MS and insulin status, the number of cases is small. At follow-up at ages 19 to 24 in the NGHS, we did not have criterion standard [17] measurement of C-peptides as well as diabetes autoantibody levels to distinguish type 1 from type 2 DM. Participants were not a random selection of the United States, as in NHANES, but came from a biracial schoolgirl population. Thus, the data, although suggestive, need to be confirmed and cannot be extrapolated to all adolescent girls. Magnetic resonance imaging [42] visceral fat measurements to estimate intra- and extravisceral fat measurements were done, but the data are not yet available. Oral glucose tolerance testing with serial measures of insulin and glucose was not done.

We conclude that insulin and MS at mean age 10 along with change in BMI over 15 years, and 15-year average insulin rank independently predict IFG + T2DM by mean age of 24, suggesting avenues for primary prevention.

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