

# Persistence of the Metabolic Syndrome Over 3 Annual Visits in Overweight Hispanic Children: Association with Progressive Risk for Type 2 Diabetes

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**Objective** To examine an association between persistent metabolic syndrome (MetS) and the risk for type 2 diabetes in overweight Hispanic children.

**Study design** A total of 73 subjects (mean age,  $11.0 \pm 1.7$  years) from a longitudinal study were classified as Never (negative for MetS at all 3 annual visits), Intermittent (positive for MetS at 1 or 2 visits), or Persistent (positive for MetS at all 3 visits). Measures included dual-energy x-ray absorptiometry, magnetic resonance imaging, the 2-hour oral glucose tolerance test, and the frequently sampled intravenous glucose tolerance test.

**Results** The Persistent group had a faster rate of fat mass gain than the Never group (20% vs 15% gain of baseline value;  $P < .05$  for time\*group interaction [time = visit]). Independent of body composition, the Persistent group increased by 70% in insulin incremental area under the curve, whereas the other groups decreased ( $P < .05$  for time\*group interaction). Despite no time\*group interactions for insulin sensitivity, acute insulin response, or disposition index, the Persistent group maintained 43% lower insulin sensitivity ( $P < .01$ ) and by visit 2 had a 25% lower disposition index ( $P < .05$ ) compared with the Never group.

**Conclusions** Patients with persistent MetS had accelerated fat gain, increased insulin response to oral glucose, and decreased sensitivity and beta cell function, indicators of progressively greater risk for type 2 diabetes (*J Pediatr* 2009;155:535-41).

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Obesity and Hispanic ethnicity are 2 independent risk factors for the development of type 2 diabetes in youth. Even in childhood, there is a linear relationship between increased body fat and decreased insulin sensitivity.<sup>1-4</sup> Furthermore, independent of body composition, Hispanic children are more insulin-resistant than Caucasian children.<sup>5</sup> National Health and Nutrition Examination Survey III data show that the metabolic syndrome (MetS), a cluster of risk factors for diabetes and cardiovascular disease,<sup>6</sup> is more common in Hispanic adolescents than in Caucasians or African American adolescents.<sup>7</sup>

MetS was found in 30% of the Study of Latino Adolescents at Risk for Diabetes (SOLAR) cohort of overweight Hispanic youth.<sup>8</sup> This cross-sectional analysis demonstrated that insulin sensitivity was inversely associated with the number of features of MetS, and that those with MetS (exhibiting 3 or more features) had 62% lower insulin sensitivity than those with no features of MetS, independent of sex, age, sexual maturation, and body composition. This relationship has not yet been evaluated over time, however.

The overall objective of the present study was to examine whether the persistence of MetS is associated with changes in risk factors for type 2 diabetes in childhood in overweight Hispanic youth. The first aim was to identify how many children in the cohort consistently had MetS at 3 annual measurements. The second aim was to determine if those with persistent MetS had differences in insulin and glucose indices over time, independent of adiposity.

AIR	Acute insulin response to glucose	IAAT	Intra-abdominal adipose tissue
ANCOVA	Analysis of covariance	IAUC	Incremental area under the curve
ANOVA	Analysis of variance	MetS	Metabolic syndrome
AUC	Area under the curve	MRI	Magnetic resonance imaging
BMI	Body mass index	OGGT	Oral glucose tolerance test
DEXA	Dual-energy x-ray absorptiometry	SAAT	Subcutaneous abdominal adipose tissue
DI	Disposition index	SI	Insulin sensitivity
FSIVGTT	Frequently sampled intravenous glucose tolerance test	SOLAR	Study of Latino Adolescents at Risk for Diabetes
HDL	High-density lipoprotein		

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## Methods

The study participants were a subset of the University of Southern California SOLAR project, a longitudinal cohort study that tracks the incidence of type 2 diabetes. Study inclusion criteria were (1) Hispanic origin, defined by all 4 grandparents being Hispanic, as determined by parental self-report; (2) family history of type 2 diabetes in at least 1 grandparent, parent, or sibling; (3) age 8 to 13 years; (4) body mass index (BMI) of at least the 85th percentile for age;<sup>9</sup> and (5) absence of diabetes, as confirmed by an oral glucose tolerance test (OGTT).<sup>10</sup> Subjects ( $n = 73$ ) were selected because they had complete data for the MetS parameters for each of the first 3 annual study visits. The mean age of the subjects was  $11.0 \pm 1.7$  years at baseline. This sample ( $n = 73$ ) did not differ at baseline from the rest of the larger initial cohort ( $n = 182$ ) in key characteristics, including age, sex, Tanner stage, BMI, body composition, fasting glucose, 2-hour glucose, and insulin sensitivity ( $P > .05$  as assessed using independent  $t$ -tests and  $\chi^2$  tests.) None of the subjects was diabetic. The University of Southern California's Institutional Review Board approved the study design. Written informed consent was obtained from parents, and assent was obtained from subjects.

Details of the longitudinal study design have been published previously.<sup>8,11,12</sup> In brief, the design involves a set of yearly clinical assessments consisting of an outpatient visit during which an OGTT is conducted and an overnight inpatient visit during which a frequently sampled intravenous glucose tolerance test (FSIVGTT) is conducted.

Each child fasted overnight and came to the General Clinical Research Center at 8:00 a.m.. With the child wearing a hospital gown, height and weight were recorded in triplicate to the nearest 0.1 cm and 0.1 kg, respectively. BMI and BMI percentile for age were calculated using the EpiInfo 2000 software, version 1.1 (Atlanta, Georgia), based on established Centers for Disease Control and Prevention normative curves.<sup>9</sup> Sitting blood pressure was measured in triplicate.<sup>13</sup> Tanner stage was coded to assess sexual maturation based on breast stage in girls and pubic hair in boys during a history and physical examination conducted by a licensed pediatric care provider.<sup>14</sup> For the OGTT, the child was given 1.75 g of oral glucose solution per kg of body weight (to a maximum of 75.0 g). Blood was collected and assayed for glucose and insulin at 5 minutes before and 15, 30, 45, 60, and 120 minutes after glucose ingestion. Impaired glucose tolerance was defined as a 2-hour postchallenge plasma glucose value of  $\geq 140$  and  $< 200$  mg/dL.<sup>10</sup> Two-hour insulin and glucose area under the curve (AUC) and incremental area under the curve (IAUC) values were calculated from the OGTT data (in mg/min/dL for glucose and  $\mu$ U/min/mL for insulin). Glucose and insulin AUC were calculated as the sum of the area of each time segment by insulin or glucose concentration, and the IAUC was calculated as the sum of the same area adjusted for the starting point.

Next, the child was admitted to the General Clinical Research Center for the inpatient visit in the afternoon and

fasted from 8:00 p.m. until testing the following morning, which began at 7:30 a.m. Sitting blood pressure was again measured in triplicate, and the values from the 2 visits were averaged. A flexible intravenous catheter was placed in each arm, and the FSIVGTT was conducted. At time 0, the child was given a 0.3-g/kg dose of glucose (25% dextrose), and samples were drawn at 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes after ingestion. At 20 minutes, a 0.02-U/kg dose of Humulin R insulin (regular insulin for human subjects; Eli Lilly, Indianapolis, Indiana) was injected. To determine insulin sensitivity (SI) and the acute insulin response to glucose (AIR), values for glucose and insulin were entered into the MINMOD Millennium 2002 program, version 5.16 (from Richard N. Bergman) (MINMOD Inc, Pasadena, California). The disposition index (DI), an index of the compensatory adaptation to insulin resistance, was calculated as the product of SI and AIR and used to approximate beta cell function. Fasting blood samples also were evaluated for triglycerides and for total and high-density lipoprotein (HDL) cholesterol using Vitros chemistry DT slides (Johnson and Johnson Clinical Diagnostics, Rochester, New York).

After the FSIVGTT, body composition was measured by a whole-body dual-energy x-ray absorptiometry (DEXA) scan performed by a certified radiology technologist using a Hologic QDR 4500 W scanner (Hologic, Bedford, Massachusetts). A urine pregnancy test was given to all female subjects before the DEXA. In addition, waist circumference, measured at the umbilicus, was recorded to the nearest 0.1 cm. Central fat distribution was measured by magnetic resonance imaging (MRI) at the LAC/USC Imaging Science Center using a GE 1.5 Signa LX-Ecospeed with a 1.5-Tesla magnet (GE Healthcare, Piscataway, New Jersey), with a single slice at the level of the umbilicus. This procedure measured intra-abdominal adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT).

No standard definition of MetS has been agreed on for children/adolescents.<sup>15,16</sup> For this analysis, MetS was categorized using a definition that we proposed previously<sup>8</sup> that applies pediatric cutoffs to the Adult Treatment Panel III definition.<sup>17</sup> MetS was defined as the presence of 3 or more of the following features: abdominal obesity (waist circumference  $\geq 90$ th percentile for age, sex, and Hispanic ethnicity from National Health and Nutrition Examination Survey III data),<sup>18</sup> hypertriglyceridemia (triglycerides  $\geq 90$ th percentile for age and sex),<sup>19</sup> low HDL cholesterol (HDL cholesterol  $\leq 10$ th percentile for age and sex),<sup>19</sup> elevated blood pressure (systolic or diastolic blood pressure  $>90$ th percentile adjusted for height, age, and sex),<sup>13</sup> and impaired glucose tolerance, as described above.

Subjects were classified into 3 groups: Never (negative for MetS at all 3 annual visits), Intermittent (positive for MetS at 1 or 2 annual visits), and Persistent (positive for MetS at all 3 annual visits). Baseline characteristics of the 3 groups were compared using the  $\chi^2$  test and analysis of variance (ANOVA) with Bonferroni correction. All subjects had complete data for the 5 features of MetS at all 3 time points; however, a subject was still included who had missing data for MRI,

DEXA, IAUC from the OGTT, or FSIVGTT (SI, AIR, or DI) measurements. At baseline, 1 subject had missing data for SI, DI, and AIR, and 6 subjects had missing MRI data. Two-year changes in adiposity as well as insulin dynamics, as assessed by SI, AIR, and DI, were analyzed by repeated-measures analysis of covariance (ANCOVA). For the ANCOVA analyses, 2 subjects had missing DEXA data, 9 had missing SAAT data, 10 had missing IAAT data, 8 had missing glucose IAUC data, 4 had missing insulin IAUC data, and 5 had missing SI, DI, and AIR data. The class variable was MetS group, and the time variable was annual number of visits (1, 2, or 3). For ANCOVA, the following covariates were included in all models: sex, baseline age, and baseline Tanner stage. Baseline lean tissue mass also was controlled for when fat mass, SAAT, or IAAT was the outcome. In the IAAT models, baseline SAAT was controlled for, and vice versa. In models in which insulin and glucose indices were evaluated, baseline body composition (fat mass and lean tissue mass) was controlled for. Models also were run with the inclusion of Tanner stage and body composition at all time points, but these covariates were not significant, and thus models including baseline values were used. For repeated-measures ANCOVA, the Mauchly test of sphericity was used to assess the form of the common covariance matrix. When the sphericity assumption was not met, the Huynh-Feldt correction was used. Data were analyzed using SPSS version 13.0 (SPSS Inc, Chicago, Illinois), and type 1 error was set at  $\alpha < 0.05$ .

## Results

Of the 73 subjects, 35 (48%) did not exhibit MetS at any of the 3 annual visits and were classified as Never, 24 (33%) exhibited MetS at 1 or 2 visits and were classified as Intermittent, and 14 (19%) exhibited MetS at all 3 visits and were

classified as Persistent. **Figure 1** (available at [www.jpeds.com](http://www.jpeds.com)) displays the persistence of each individual feature by MetS group. The most persistent feature was high waist circumference, followed by low HDL cholesterol and high triglycerides. The percentage of subjects exhibiting persistent MetS features was incremental by MetS group, with the lowest percentage in the Never group and the highest percentage in the Persistent group. The number of features seen in each MetS group also was incremental, with the Never group having an average of 1.02 features, the Intermittent group having an average of 2.18 features, and the Persistent group having an average of 3.48 features (data not shown).

**Table I** summarizes baseline unadjusted descriptive characteristics of the subjects by MetS group. Subject age did not differ across the 3 groups. The Never group had fewer male subjects ( $P < .05$ ) and lower BMI compared with the other 2 groups ( $P < .05$ ). In addition, the Never group had lower fat mass ( $P < .05$ ) and lean mass ( $P < .01$ ) compared with the Intermittent group. There was an overall group difference in SAAT ( $P < .05$ ), but no differences in IAAT ( $P > .05$ ). Subjects in the Persistent group had a lower mean Tanner stage than those in the other groups, indicating that they were less sexually mature ( $P < .05$ ). **Table I** also compares the features of MetS at baseline in the 3 groups. As expected based on the group definitions, the Never group had the lowest waist circumference, blood pressure, and triglyceride levels and the highest HDL cholesterol levels of the 3 groups ( $P < .05$ ), but 2-hour glucose values did not differ by group.

**Table II** presents baseline unadjusted insulin- and glucose-related indices for the 3 groups. The Intermittent group had a higher fasting insulin level than the Never group ( $P < .01$ ), but fasting glucose, glucose IAUC, and insulin IAUC values did not differ among the 3 groups. SI was highest in the Never group ( $P < .05$ ), but AIR and DI did not differ by group.

**Table I.** Baseline unadjusted descriptive characteristics and individual MetS features by MetS group in overweight Hispanic children

Variable		Never (N) (n = 35)	Intermittent (I) (n = 24)	Persistent (P) (n = 14)	Significant comparisons		
					N vs I	N vs P	I vs P
Male sex, %	Pearson $\chi^2$ *	31.40%	62.50%	64.30%			
	Omnibus test						
Tanner stage	*	2.43 ± 1.20	2.54 ± 1.50	1.43 ± 1.09		*	*
Age, years		11.0 ± 1.7	11.6 ± 1.8	10.4 ± 1.4			
BMI, kg/m <sup>2</sup>	**	25.7 ± 4.5	29.6 ± 6.1	29.7 ± 5.0	*	*	
BMI percentile	***	95.2 ± 3.9	97.8 ± 2.1	98.7 ± 1.0	**	**	
Total fat mass, kg	*	20.5 ± 8.1	27.1 ± 11.3	26.8 ± 10.9	*		
Total lean tissue mass, kg	**	33.0 ± 7.8	41.5 ± 11.9	35.8 ± 9.6	**		
Waist circumference, cm	**	81.4 ± 11.5	91.1 ± 12.3	91.0 ± 14.6	*		
SAAT, cm <sup>2</sup>	*	280.4 ± 111.2 (n = 31)	347.2 ± 131.3 (n = 23)	372.1 ± 144.6 (n = 13)			
IAAT, cm <sup>2</sup>		44.7 ± 20.0 (n = 31)	46.2 ± 18.7 (n = 23)	54.8 ± 19.3 (n = 13)			
Systolic blood pressure, mm Hg	***	105.1 ± 9.1	110.6 ± 8.5	116.5 ± 6.4	*	***	
Diastolic blood pressure, mm Hg	**	60.8 ± 4.6	61.9 ± 5.2	65.9 ± 3.7		**	*
HDL cholesterol, mg/dL	***	44.6 ± 10.5	36.2 ± 6.6	32.6 ± 4.8	**	***	
Triglycerides, mg/dL	***	90.6 ± 39.9	126.5 ± 43.9	143.0 ± 53.9	**	**	
Two-hour glucose, mg/dL		124.0 ± 17.6	123.0 ± 16.3	131.1 ± 15.2			

Never, negative for MetS at all 3 annual visits. Intermittent, positive for MetS at 1 or 2 visits. Persistent, positive for MetS at all 3 visits. The  $\chi^2$  test was used for sex and Tanner stage comparisons; data are percentages or medians. ANOVA was performed to compare means with Bonferroni corrections for multiple comparisons; data are means ± standard deviations.

\* $P < .05$ .

\*\* $P < .01$ .

\*\*\* $P < .001$ .

**Table II.** Baseline unadjusted indices of insulin and glucose by MetS group in overweight Hispanic children

Variable	Ombibus test	Never (N) (n = 35)	Intermittent (I) (n = 24)	Persistent (P) (n = 14)	Significant comparisons		
					N vs I	N vs P	I vs P
Fasting glucose, mg/dL		89.9 ± 6.9	91.5 ± 6.3	93.6 ± 6.3			
2 hour glucose, mg/dL		124.0 ± 17.6	123.0 ± 16.3	131.1 ± 15.2			
Glucose IAUC, mg/min/dL		87.4 ± 36.1	74.5 ± 31.9	94.5 ± 45.3			
Fasting insulin, $\mu\text{U/mL}$	**	11.8 ± 6.7	20.9 ± 11.8	18.0 ± 10.4	**		
Two-hour insulin, $\mu\text{U/mL}$		120.0 ± 94.2	164.8 ± 142.4	157.4 ± 110.8			
Insulin IAUC, $\mu\text{U/min/mL}$		237.7 ± 144.8	285.1 ± 226.5	299.8 ± 132.4			
Insulin sensitivity ( $\times 10^{-4} \text{ min}^{-1}/\mu\text{U/mL}$ )	**	2.7 ± 1.5 (n = 34)	1.7 ± 1.0	1.6 ± 0.6	**	*	
Acute insulin response ( $\mu\text{U/mL} \times 10 \text{ min}$ )		1357 ± 1020 (n = 34)	2192 ± 1709	1736 ± 941			
Disposition index ( $\times 10^{-4} \text{ min}^{-1}$ )		2660 ± 1341 (n = 34)	2597 ± 1067	2387 ± 915			

Never, negative for MetS at all 3 annual visits. Intermittent, positive for MetS at 1 or 2 visits. Persistent, positive for MetS at all 3 visits. ANOVA was performed to compare means with Bonferroni corrections for multiple comparisons; data are means  $\pm$  standard deviations.

\* $P < .05$ .

\*\* $P < .01$ .

**Table III** summarizes results of the repeated-measures ANOVA. Although overall BMI percentile did not change significantly over time, the Never group maintained a lower adjusted BMI percentile compared with the other groups ( $P < .05$ ). The Persistent group gained fat mass at a faster rate than the Never group (**Figure 2, A**), with a 20% versus 15% increase from baseline value by visit 3 ( $P = .024$  for time\*group interaction). The Persistent group also maintained a significantly higher level of SAAT than the Never group ( $P = .048$ ), but this difference was stable over time. IAAT was not significantly affected by time, group status, or an interaction of time\*group status.

Repeated-measures ANCOVA also revealed longitudinal differences in indices related to insulin and glucose independent of covariates, including body composition. The Persistent group maintained higher fasting glucose, 2-hour glucose, and glucose AUC values than the other 2 groups ( $P < .05$ ), but these differences were stable over time. However, changes in 2-hour insulin and insulin IAUC values over time were significantly associated with MetS group; the Persistent group exhibited  $> 70\%$  increases in both, whereas the other 2 groups had overall decreases in both (**Figure 2, B**;  $P < .05$  for time\*group interaction). In addition, although all subjects regardless of group exhibited a decline in adjusted SI over time ( $P = .001$ ), those in the Persistent group remained 43% less insulin-sensitive on average compared with those in the Never group (**Figure 2, C**;  $P = .006$ ). Furthermore, despite no significant differences in baseline DI, by visit 2, the Persistent group had a 25% lower adjusted DI than the Never group, and this difference was maintained through visit 3 (**Figure 2, D**;  $P = .02$ ). However, the rates of change did not differ by group for DI or for AIR (time\*group interaction  $> 0.05$ ), and there were no intergroup differences in AIR.

## Discussion

This study examined the persistence of MetS over time during childhood, focusing specifically on associations with the risk for type 2 diabetes in overweight Hispanic youth. In

a study by Goodman et al,<sup>20</sup> 1098 adolescents (52% Caucasian, 47% African American, and 2% Hispanic) were evaluated for MetS at baseline (average age, 15 years) and at follow-up 3 years later. The authors concluded that clinical categorization of MetS was not stable, and that the syndrome has limited clinical utility for adolescents; however, they did not evaluate associations with insulin sensitivity and beta cell function.<sup>20</sup> In another study, Weiss et al<sup>21</sup> assessed for MetS at 2 time points an average of 22 months apart in a subsample of 77 subjects age 4 to 20 years at baseline. Although demographic information was not given for the subsample, the larger study sample was 27% Hispanic. The authors found that 71% of the subjects who had MetS at the first assessment also had it at the second assessment. In addition, 8 subjects who had impaired glucose tolerance and MetS at the first assessment developed type 2 diabetes by the second assessment.

In addition to these 2 studies that evaluated the persistence of MetS, several other studies have evaluated either predictors of MetS in childhood or associations between childhood MetS and risk for type 2 diabetes later in life. In a study of 154 Caucasian girls who were assessed for adiposity at age 5, 7, 9, 11, and 13 years and for MetS at age 13 only, Ventura et al<sup>22</sup> found that increases in fat mass and BMI across childhood were predictive of MetS risk at age 13. In a study of 1604 American Indians, Franks et al<sup>23</sup> found that a composite score of MetS features in 5- to 19-year-olds was predictive of the development of type 2 diabetes. Morrison et al<sup>24</sup> found that in a sample of youth (72% Caucasian and 28% African American; age 5 to 19 years at baseline), MetS in childhood was a significant predictor of type 2 diabetes 25 to 30 years later. To the best of our knowledge, our study is the first to show that progressive risk for type 2 diabetes is evident with persistent MetS over just 3 consecutive annual measurements during childhood.

The underlying pathophysiology behind the progressive risk for type 2 diabetes in the Persistent group, particularly in comparison with the Never group, comprises increasing adiposity, consistently lower SI, and impaired ability of pancreatic beta cells to compensate by increasing insulin secretion—that is, DI, which was lower by visit 2 and remained

**Table III.** Repeated-measures ANOVA for adiposity measures and insulin/glucose indices by MetS group in overweight Hispanic children

	Adjusted values			Time	MetS group				Time*group
	Baseline (visit 1)	1 year follow-up (visit 2)	2-year follow-up (visit 3)		Omnibus test	Group contrasts			
						N vs I	N vs P	I vs P	
BMI, kg/m <sup>2†</sup>				0.642	0.001	*	***		0.445
Never (n = 35)	25.7 ± 3.3	26.8 ± 3.2	28.8 ± 3.6						
Intermittent (n = 24)	29.6 ± 3.4	31.3 ± 3.5	31.5 ± 3.6						
Persistent (n = 14)	29.7 ± 2.8	32.0 ± 2.8	33.2 ± 2.9						
BMI percentile <sup>†</sup>				0.312	<0.001	**	***		0.481
Never (n = 35)	95.2 ± 0.9	95.2 ± 0.7	94.0 ± 0.9						
Intermittent (n = 24)	97.8 ± 0.9	98.0 ± 0.8	97.1 ± 1.0						
Persistent (n = 14)	98.7 ± 0.9	99.0 ± 0.7	98.9 ± 0.8						
Fat mass, kg <sup>†</sup>				0.066	0.106		*		0.024
Never (n = 35)	20.5 ± 6.7	22.5 ± 6.2	23.6 ± 5.7						
Intermittent (n = 24)	27.1 ± 9.2	30.5 ± 8.6	30.6 ± 7.5						
Persistent (n = 12)	27.2 ± 8.5	30.7 ± 7.6	32.8 ± 6.7						
SAAT, cm <sup>2†</sup>				0.059	0.138		*		0.542
Never (n = 31)	280.4 ± 90.2	307.2 ± 91.9	320.8 ± 85.3						
Intermittent (n = 21)	356.1 ± 118.5	416.1 ± 117.4	412.4 ± 105.0						
Persistent (n = 12)	370.1 ± 113.9	422.1 ± 114.1	442.6 ± 101.5						
IAAT, cm <sup>2</sup>				0.053	0.342				0.268
Never (n = 31)	44.7 ± 9.7	36.4 ± 7.2	36.4 ± 11.0						
Intermittent (n = 21)	46.5 ± 11.2	48.9 ± 8.4	55.7 ± 13.0						
Persistent (n = 11)	51.6 ± 11.3	47.9 ± 6.9	55.2 ± 11.5						
Fasting glucose, mg/dL				0.408	0.012		**	*	0.481
Never (n = 35)	89.9 ± 2.9	89.7 ± 0.7	91.3 ± 1.5						
Intermittent (n = 24)	91.5 ± 3.1	92.3 ± 0.9	93.2 ± 2.5						
Persistent (n = 14)	93.6 ± 2.5	96.2 ± 0.6	98.6 ± 1.7						
Two-hour glucose, mg/dL				0.045	<0.001	*	***	*	0.251
Never (n = 35)	124 ± 4.8	122.7 ± 4.3	116.5 ± 5.4						
Intermittent (n = 24)	123.0 ± 6.1	129.3 ± 6.7	127.2 ± 5.5						
Persistent (n = 14)	131.1 ± 6.1	140.0 ± 4.9	136.8 ± 4.6						
Glucose IAUC, mg/min/dL				0.461	0.005		**	*	0.238
Never (n = 33)	85.7 ± 13.8	81.7 ± 12.0	69.9 ± 9.2						
Intermittent (n = 20)	72.4 ± 20.0	81.7 ± 16.2	79.6 ± 12.5						
Persistent (n = 12)	94.6 ± 19.2	102.3 ± 18.0	103.0 ± 13.9						
Fasting insulin, μU/mL				0.031	0.146				0.196
Never (n = 34)	11.5 ± 3.5	15.2 ± 3.1	16.1 ± 5.1						
Intermittent (n = 23)	20.1 ± 5.1	20.3 ± 4.5	16.8 ± 5.8						
Persistent (n = 14)	18.0 ± 5.0	25.6 ± 3.7	25.7 ± 4.5						
Two-hour insulin, μU/mL				0.828	0.007		**	*	0.029
Never (n = 34)	125.1 ± 40.9	159.5 ± 44.7	93.8 ± 44.5						
Intermittent (n = 23)	171.0 ± 48.5	171.6 ± 57.6	157.4 ± 52.3						
Persistent (n = 14)	157.4 ± 40.2	286.9 ± 40.6	281.2 ± 43.0						
Insulin IAUC, μU/min/mL <sup>†</sup>				0.025	0.025		*	*	0.012
Never (n = 34)	234.3 ± 68.1	293.8 ± 69.1	210.6 ± 83.8						
Intermittent (n = 22)	289.9 ± 92.0	311.2 ± 94.4	277.7 ± 104.8						
Persistent (n = 13)	302.6 ± 74.2	449.4 ± 76.1	516.0 ± 98.9						
SI, ×10 <sup>-4</sup> min <sup>-1</sup> /μU/mL <sup>†</sup>				0.001	0.019		**		0.872
Never (n = 32)	2.78 ± 0.7	2.04 ± 0.5	1.94 ± 0.3						
Intermittent (n = 23)	1.71 ± 0.9	1.43 ± 0.6	1.37 ± 0.4						
Persistent (n = 13)	1.7 ± 0.8	1.11 ± 0.5	1.06 ± 0.3						
AIR, μU/mL × 10 min				0.106	0.506				0.302
Never (n = 32)	1336.4 ± 466.5	1493.5 ± 475.8	1519.0 ± 296.8						
Intermittent (n = 23)	2211.3 ± 684.7	2132.5 ± 634.7	1882.3 ± 381.0						
Persistent (n = 13)	1568.0 ± 740.1	1973.1 ± 649.2	1930.2 ± 410.7						
DI, ×10 <sup>-4</sup> min <sup>-1</sup>				0.419	0.044		*	*	0.482
Never (n = 32)	2606.7 ± 491.3	2454.5 ± 562.5	2319.0 ± 410.8						
Intermittent (n = 23)	2607.6 ± 634.9	2313.9 ± 714.3	2066.8 ± 435.8						
Persistent (n = 13)	2368.3 ± 404.7	1845.3 ± 361.1	1669.6 ± 233.1						

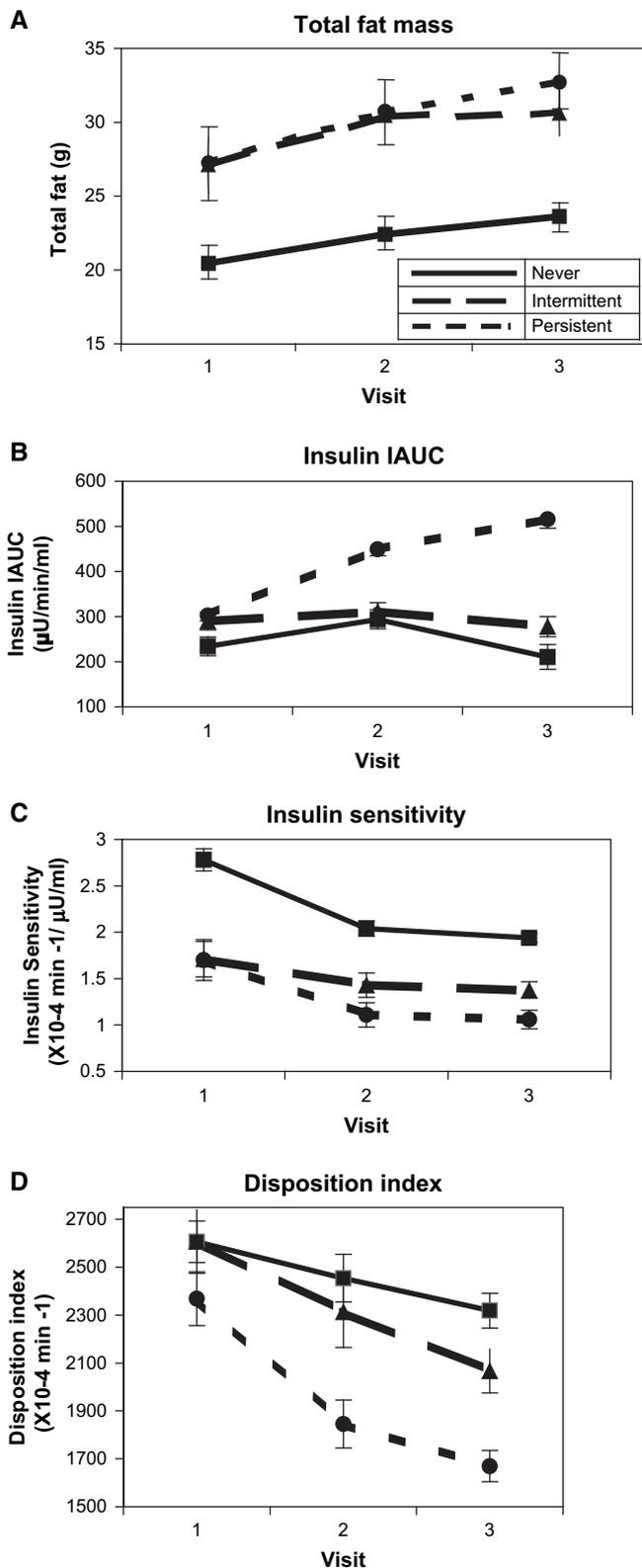
Never, negative for MetS at all 3 annual visits. Intermittent, positive for MetS at 1 or 2 visits. Persistent, positive for MetS at all 3 visits. Repeated-measures ANOVA was used to compare changes in insulin and glucose dynamics over visits 1 to 3; data are means ± standard deviations. All analyses are adjusted for sex, baseline age, and Tanner stage. Total lean tissue mass also was controlled for in the total fat mass model, and total lean and total fat were controlled for in all insulin and glucose indices models.

\*P < .05.

\*\*P < .01.

\*\*\*P < .001.

†The sphericity assumption was violated, and Huynh-Feldt correction was used.



**Figure 2.** Changes in fat mass and insulin/glucose indices over 3 annual visits by MetS group in overweight Hispanic children. **A**, Total fat mass (n = 71). **B**, Insulin IAUC (n = 69). **C**, Insulin sensitivity (n = 68). **D**, DI (n = 68).

consistently lower through visit 3. Other research has shown that insulin resistance and impaired insulin secretion are independent predictors of the development of type 2 diabetes in adult Pima Indians and Hispanics.<sup>25-27</sup> Although all of the subjects in our analysis exhibited an overall decline in SI across the 3 annual visits, the Persistent group showed a dramatically accelerated increase in insulin response to oral glucose, supporting the conclusion that these subjects are becoming progressively more insulin-resistant than those in the other 2 groups.

It is important to note that all of the subjects in our analysis, regardless of MetS group status, had a lower SI than normal-weight children their age. To put our results into context, in a previous analysis of a multiethnic group of children (mean age, 9.6 years), Goran et al<sup>28</sup> found an inverse relationship between fat mass and SI independent of family history of type 2 diabetes. This group of children had an average BMI of approximately 20 and an average SI of approximately 6. In comparison, in our study the average baseline SI was 2.7 in the Never group, 1.7 in the Intermittent group, and 1.6 in the Persistent group. Therefore, although all of our subjects were relatively insulin-resistant, those with more MetS features were more dramatically so. It also is noteworthy that at baseline, the Intermittent and Persistent groups were fairly comparable in terms of adiposity and insulin/glucose indices, including SI; however, by following these groups across 3 visits, we found that the Persistent group had stronger associations with progressive diabetes risk.

Considering that the Persistent group was less sexually mature (as indicated by Tanner staging) at baseline compared with the other 2 groups, an important question that arises is whether the Persistent group progressed through puberty at a different rate than the other groups, which could have influenced their metabolic health. To answer this question, we assessed the changes in Tanner stage in the 3 groups by repeated-measures ANOVA (data not shown). We found that although the Persistent group started at a lower Tanner stage of 1.4, compared with 2.4 and 2.5 in the other groups, all groups progressed through the Tanner stages at the same rates; that is, we found no time\*group interaction in Tanner stage over time. Nonetheless, we included Tanner stage as a covariate in all of the adiposity and glucose/insulin models considered, to ensure that our results were not driven by differences in pubertal development.

Our findings have several important implications for the clinical screening of overweight youth for associated metabolic comorbidities. Although current consensus statements include screening for both type 2 diabetes and features of MetS,<sup>6,29</sup> the value of repetitive assessment for MetS in youth has been unclear. Our findings indicate that assessing overweight Hispanic children for MetS on a yearly basis can help identify those at particular risk for type 2 diabetes. Yearly MetS assessment is achievable and relatively inexpensive. In comparison, FSIVGTT, which takes 3 hours to complete and requires the injection of glucose and insulin, is not a practical screening tool. Logistic considerations must be taken into account when determine which definition of

MetS to use, however. For example, in a clinic setting, it would be easier to measure fasting blood glucose rather than 2-hour glucose from an OGTT, as we used in this study. To address this concern, our group conducted a cross-sectional comparison in our cohort using 3 published pediatric definitions for MetS,<sup>7,8,21</sup> including a definition that used fasting glucose rather than 2-hour glucose,<sup>7</sup> and found that the inverse relationship between MetS features and SI was maintained regardless of the definition used.<sup>15</sup>

A limitation of the present study is the relatively small overall sample size and the uneven sample sizes of the MetS groups, which could preclude additional findings. In addition, the generalizability of our findings is limited to Hispanic youth in a similar age range (~8 to 13 years) with a family history of diabetes. However, these limitations are offset by the strength of the longitudinal study design, along with the well-defined study population and the use of rigorous measures of metabolic status, such as DEXA for adiposity and FSIVGTT for SI. ■

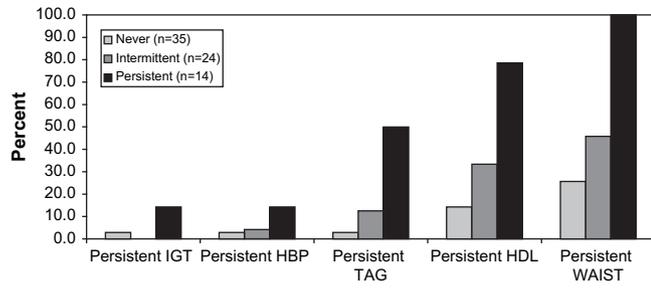
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Never=negative for metabolic syndrome at all 3 annual visits, Intermittent=positive for metabolic syndrome at 1 or 2 visits. Persistent = positive for metabolic syndrome at all 3 visits.

**Figure 1.** Persistence of each MetS feature by MetS group.