Prevalence and Determinants of Insulin Resistance Among U.S. Adolescents

A population-based study

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OBJECTIVE — We sought to examine the distribution of insulin and homeostasis model assessment of insulin resistance (HOMA-IR) and associations of HOMA-IR with sex, race/ethnicity, age, and weight status, as measured by BMI, among U.S. adolescents.

RESEARCH DESIGN AND METHODS — Of 4,902 adolescents aged 12–19 years who participated in the National Health and Nutrition Examination Survey 1999–2002, analysis was performed for a nationally representative subsample of 1,802 adolescents without diabetes who had fasting laboratory measurements. The main outcome measure was HOMA-IR, calculated from fasting insulin and glucose and log transformed for multiple linear regression analyses.

RESULTS — In adjusted regression models that included age and weight status, girls had higher HOMA-IR than boys and Mexican-American children had higher HOMA-IR levels than white children. There were no significant differences in adjusted HOMA-IR between black and white children. Obese children (BMI ≥95th percentile) had significantly higher levels of HOMA-IR compared with children of normal weight (BMI <85th percentile) in adjusted comparisons (mean HOMA-IR 4.93 [95% CI 4.56–5.35] vs. 2.30 [2.21–2.39], respectively). Weight status was by far the most important determinant of insulin resistance, accounting for 29.1% of the variance in HOMA-IR. The prevalence of insulin resistance in obese adolescents was 52.1% (95% CI 44.5–59.8).

CONCLUSIONS — Obesity in U.S. adolescents represents the most important risk factor for insulin resistance, independent of sex, age, or race/ethnicity. The prevalence of insulin resistance in obese children foreshadows a worrisome trend for the burden of type 2 diabetes in the U.S.

Diabetes Care **29:2427–2432, 2006**

The pathogenesis of type 2 diabetes in children is hypothesized to be related to two principal factors: insulin resistance and impaired insulin secretion (1). Insulin resistance represents an insensitivity of the peripheral tissues (e.g., muscle, liver, adipose tissue) to the effects of insulin. To maintain glucose homeostasis, pancreatic β-cells compensate for insulin resistance by augmenting insulin secretion, leading to a state of chronic hyperinsulinemia. However, the progressive failure of the β-cells to maintain adequate insulin secretion is believed to result in the development of type 2 diabetes (2). Longitudinal studies in adults have demonstrated that insulin resistance is strongly predictive of the development of type 2 diabetes (3). Furthermore, studies in obese children have shown that insulin resistance is associated with abnormalities in glucose metabolism, such as impaired glucose tolerance or type 2 diabetes (4). Therefore, there is increasing recognition of the important role of insulin resistance in the pathogenesis of type 2 diabetes in children (1,2,5).

Given that insulin resistance represents an important risk factor for development of type 2 diabetes, identification of children with insulin resistance has been proposed as a strategy for identifying high-risk children for targeted diabetes prevention interventions (6). The gold-standard test for insulin resistance includes the hyperinsulinemic-euglycemic clamp (7), and another accepted method is the minimal-model analysis frequently sampled intravenous glucose tolerance test (FSIVGTT) (8). These tests are invasive, labor intensive, and expensive, which discourages their use in large population-based epidemiologic studies. A simpler and more practical method to measure insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR), was therefore developed for application in large epidemiologic studies (9).

HOMA-IR is an estimate of insulin resistance derived from fasting glucose and insulin levels, with higher levels representing greater degrees of insulin resistance. HOMA-IR has been validated as a surrogate measure of insulin resistance in nondiabetic children, with studies showing correlations as high as 0.91 with clamp or FSIVGTT measures (10–13).

Studies (14,15) in children have established that increasing BMI is associated with an increase in insulin resistance. Given the alarming rise in obesity rates among youth in the U.S., there is great concern that diabetes incidence will shadow this trend. However, studies to evaluate insulin resistance in population-based samples of children are limited. We sought to evaluate the distribution of HOMA-IR in a diverse group of U.S. ado-

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Received for publication 31 March 2006 and accepted in revised form 16 August 2006.

Abbreviations: FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; NFG, normal fasting glucose; NHANES, National Health and Nutrition Examination Survey.

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

DOI: 10.2337/dc06-0709

lescents who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002.

RESEARCH DESIGN AND METHODS

— NHANES is a cross-sectional, nationally representative examination survey of the U.S. civilian noninstitutionalized population (16,17). NHANES uses a stratified multistage probability sampling design, oversampling adolescents aged 12–19 years, non-Hispanic blacks, and Mexican Americans to provide reliable statistical estimates for these subpopulations. Of the 4,902 adolescents aged 12–19 years in the study, a subsample had glucose and insulin levels measured ($n = 2015$). Adolescents who had self-reported diabetes ($n = 10$), were pregnant ($n = 39$), were using medications that would interfere with glucose metabolism (antihypoglycemics, steroids, or androgens) ($n = 29$), and who did not fast for at least 8 h ($n = 133$) were excluded, which left 1,804 adolescents. Because two individuals had previously undiagnosed diabetes (fasting glucose >126 mg/dl), 1,802 adolescents were used for the analysis, including 222 with impaired fasting glucose (100 ≤ glucose < 126 mg/dl) (10.7% of the weighted population), and 1,580 with normal fasting glucose (NFG; glucose <100 mg/dl) (89.3% of the weighted population).

Because studies have shown that HOMA-IR may serve as a valuable surrogate measure of insulin resistance in nondiabetic children (12), we chose to include adolescents with both NFG and impaired fasting glucose for this analysis, reporting an estimate of HOMA-IR reflective of the entire nondiabetic population. We also performed analyses of only children with NFG. Despite slightly lower mean HOMA-IR levels, the relationship of HOMA-IR with the demographic and weight variables remained similar (data available from the authors upon request).

Mexican-American adolescents with fasting laboratory measurements had lower mean BMI compared with those without (23.8 vs. 24.5, respectively, $P = 0.04$), and a lower proportion of black females had fasting laboratory measurements than those without (45.5 vs. 52.8%, respectively, $P = 0.004$). Otherwise, there were no significant differences in age, sex, and BMI between groups for the overall sample and among racial groups.

Sociodemographic information was obtained through household interviews administered in English or Spanish. A digital stadiometer was used to measure height, and a digital weight scale was used to measure weight; these instruments were calibrated on a weekly and daily basis, respectively. For height measurements, adolescents stood with the heels of both feet together and feet flat on the floor, and for weight measurements they were undressed, wearing underwear and paper gowns (18).

For determination of fasting status, a detailed fasting questionnaire was administered (19). Fasting samples for insulin and plasma glucose were obtained by venipuncture and analyzed at a central laboratory at the University of Missouri-Columbia. Samples were allowed to clot at room temperature for 15–30 min, were centrifuged, and the serum was frozen at −20° for insulin (20) and −70° for glucose (21). Analysis of samples was performed up to 1 week after the samples were drawn. Insulin was measured using the Pharmacia Insulin RIA kit (Pharmacia Biotech, Uppsala, Sweden; interassay coefficient of variation [CV] <4.9%; intraassay CV <5.0%) with a cross-reactivity with proinsulin of ~40% (20). Plasma glucose was measured using modified hexokinase enzymatic methods (21).

Data analysis

HOMA-IR was calculated by dividing the product of insulin (microunits per milliliter) and glucose (millimoles per liter) by 22.5 (22). BMI was converted to age- and sex-standardized percentiles based on the Centers for Disease Control and Prevention 2000 growth charts, which are not race specific (23). Adolescents were classified as normal weight if BMI was <85th percentile, overweight if BMI was ≥85th and <95th percentile, or obese if BMI was ≥95th percentile.

Means and SEs for insulin, glucose, and HOMA-IR were calculated using Stata 9.0 (Stata, College Station, TX), which applies appropriate sampling weights to adjust for the complex multicluster sample design, oversampling, and nonresponse. Separate sampling weights were created to reflect the additional stage of sampling and the additional nonresponse for the subsample of adolescents with fasting glucose and insulin. These weights were used for the analysis, and therefore each subsample is a nationally representative sample (24). Taylor series linearization was used for variance estimation. Because of the right-skewed distribution of HOMA-IR, weighted linear regression was performed on log-transformed HOMA-IR, controlling for age, sex, race, and weight status. Socioeconomic status, coded as a total family income less than or greater than or equal to $20,000, was evaluated. Because there were no significant differences in log HOMA-IR between groups in the unadjusted comparisons and within the full model, the socioeconomic status variable was omitted in order to maintain the most parsimonious model. Postregression adjustment of the log-transformed HOMA-IR was performed to convert log estimates back to HOMA-IR values for the demographic and weight groups (25). Boot strapping was used to generate 95% CIs for the adjusted HOMA-IR values.

Insulin resistance was defined based on a number of different thresholds, including HOMA-IR >4.39 (upper 2.5 percentile or >2 SD above mean HOMA-IR for normal-weight adolescents with NFG in this study), HOMA-IR >3.29 (upper quartile of insulin resistance for all adolescents) (26), HOMA-IR >3.16 (11), and HOMA-IR >3.99 (27). We calculated the upper 2.5 percentile based on non–log-transformed HOMA-IR for normal-weight subjects with NFG. Weighted prevalence estimates of insulin resistance were calculated for normal-weight, overweight, and obese children.

RESULTS

— In the study population, 12.9% of adolescents were overweight and 16.3% were obese. Table 1 shows demographic characteristics of the study population and the distribution of weight status among the various racial/ethnic groups. There were no statistical differences in weight status by sex or age. However, a greater proportion of Mexican-American and black adolescents were overweight or obese compared with non-Hispanic white adolescents.

The distribution of fasting glucose within the population was narrow, with a mean value of 91.4 mg/dl (95% CI 91.0–91.9). The correlation between HOMA-IR and insulin levels was high ($r = 0.88$).

Table 2 shows unadjusted insulin and HOMA-IR levels and adjusted HOMA-IR levels stratified by sex, race, weight status, and age. For unadjusted comparisons, there were no significant differences in insulin or HOMA-IR by sex, but after adjustment for race, age, and weight status, female subjects had significantly higher mean HOMA-IR than male subjects ($P = 0.02$). Unadjusted insulin and HOMA-IR

Table 1—*Characteristics of the study population*

Characteristic	Overall population	BMI <85th percentile	BMI ≥85th and <95th percentile	BMI ≥95th percentile	*P* value across weight status
Sex					0.33
Male	939 (52.0)	605 (68.0)	143 (14.6)	184 (17.4)	
Female	863 (48.0)	564 (73.0)	136 (11.5)	156 (15.5)	
Race					0.03
Non-Hispanic white	490 (63.1)	357 (73.6)	57 (11.4)	72 (15.0)	
Black	510 (14.0)	304 (59.2)	95 (19.0)	109 (21.9)	
Mexican American	672 (10.6)	422 (63.7)	106 (15.9)	138 (20.4)	
Age (years)					0.32
12	237 (12.9)	152 (72.0)	37 (12.3)	47 (15.6)	
13	258 (13.2)	149 (62.1)	51 (18.8)	58 (19.1)	
14	219 (11.8)	137 (73.8)	32 (9.4)	49 (16.7)	
15	196 (12.1)	128 (69.0)	34 (16.5)	33 (14.5)	
16	228 (12.4)	150 (69.3)	31 (13.1)	45 (17.6)	
17	244 (14.3)	171 (77.5)	31 (9.3)	39 (13.2)	
18	208 (10.9)	141 (73.8)	35 (13.7)	31 (12.5)	
19	212 (12.5)	141 (65.5)	28 (11.9)	40 (22.6)	

Data are *n* (weighted %).

values were higher in black and Mexican-American adolescents compared with white adolescents. After adjustment for age, sex, and weight status, Mexican-American adolescents had higher mean HOMA-IR levels than white adolescents ($P = 0.001$), but no significant differences in HOMA-IR were found between black and white adolescents ($P = 0.19$).

Unadjusted and adjusted mean HOMA-IR values for obese adolescents were 5.18 (95% CI 4.74–5.63) and 4.93 (4.56–5.35), respectively. After adjustment for sex, age, and race, overweight ($P < 0.001$) and obese ($P < 0.001$) adolescents had higher HOMA-IR levels compared with adolescents of normal weight (Table 2).

Table 2 shows unadjusted and adjusted HOMA-IR levels by age for the overall study population. Adolescents aged 14 years had higher HOMA-IR levels than those aged 12 years for unadjusted and adjusted values. Table 3 shows mean HOMA-IR values for each age stratified by sex and weight status. HOMA-IR values appear to peak at age 14 years in boys and age 13 years in girls. Among normal-weight and overweight adolescents, HOMA-IR values did not differ substantially between ages; however, there was an apparent peak at age 14 years among obese adolescents.

In a linear regression model predicting log HOMA-IR, weight status alone accounted for 29.1% of the variance. The addition of covariates of age, sex, and race/ethnicity only resulted in a slight increase in the explained variance to 31.2%.

Figure 1 shows the prevalence of insulin resistance stratified by weight status based on different thresholds for defining insulin resistance. Regardless of the definition used, the prevalence of insulin resistance was substantially higher in obese children compared with normal-weight children. Using a definition of insulin resistance of HOMA-IR >4.39, the prevalence of insulin resistance in obese children was 52.1% (95% CI 44.5–59.8).

CONCLUSIONS — We present the first study to report the distribution of HOMA-IR, a validated measure of insulin resistance, for a population-based, racially diverse, nationally representative sample of U.S. adolescents, finding that HOMA-IR is markedly higher in obese compared with normal-weight adolescents. Although previous studies have demonstrated that insulin resistance in children/adolescents is influenced by a

Table 2—*Mean HOMA-IR values by demographic characteristics*

	Unadjusted insulin (95% CI) (μU/ml)	Unadjusted HOMA-IR (95% CI)	Adjusted HOMA-IR (95% CI)
Overall	12.57 (12.00–13.15)	2.87 (2.73–3.01)	—
Sex			*
Male	12.15 (11.37–12.93)	2.84 (2.64–3.03)	2.74 (2.61–2.89)
Female	13.03 (12.23–13.84)	2.91 (2.71–3.10)	2.97 (2.82–3.11)†
Race			‡
White	11.88 (11.09–12.67)	2.72 (2.53–2.91)	2.76 (2.63–2.91)
Black	14.19 (13.37–15.01)§	3.17 (2.96–3.37)‖	2.90 (2.76–3.05)
Mexican American	14.04 (13.07–15.01)¶	3.27 (3.04–3.50)¶	3.08 (2.94–3.23)§
Weight status			#
BMI <85th percentile	10.09 (9.59–10.58)	2.28 (2.16–2.39)	2.30 (2.21–2.39)
BMI ≥85th and <95th percentile	13.56 (12.69–14.42)¶	3.09 (2.86–3.32)¶	3.16 (2.95–3.40)¶
BMI ≥95th percentile	22.28 (20.44–24.13)¶	5.18 (4.74–5.63)¶	4.93 (4.56–5.35)¶
Age (years)			**
12	12.30 (11.00–13.60)	2.84 (2.52–3.16)	2.78 (2.53–3.05)
13	12.94 (11.55–14.34)	2.94 (2.63–3.25)	2.82 (2.57–3.08)
14	14.81 (12.75–16.88)†	3.43 (2.92–3.94)††	3.27 (2.97–3.61)‡‡
15	12.20 (10.72–13.69)	2.80 (2.44–3.16)	2.87 (2.63–3.15)
16	11.90 (10.93–12.87)	2.69 (2.45–2.92)	2.73 (2.55–2.95)
17	11.84 (10.65–13.04)	2.66 (2.38–2.94)	2.76 (2.57–2.97)
18	11.79 (10.53–13.04)	2.67 (2.37–2.98)	2.77 (2.54–3.01)
19	12.89 (11.74–14.05)	2.96 (2.67–3.24)	2.81 (2.58–3.08)

For unadjusted and adjusted comparisons, reference groups are male, white, normal weight, and children aged 12 years. *Adjusted for race, weight status, and age. ‡Adjusted for sex, weight status, and age. #Adjusted for sex, race, and age. **Adjusted for sex, race, and weight status. †$P = 0.02$; §$P = 0.001$; ‖$P = 0.005$; ¶$P < 0.001$; ††$P = 0.04$; ‡‡$P = 0.002$.

Table 3—*Unadjusted HOMA-IR (95% CI) stratified by sex and weight status*

Age (years)	Male	Female	BMI <85th percentile	BMI ≥85th and <95th percentile	BMI ≥95th percentile
12	2.45 (2.12–2.78)	3.21 (2.73–3.69)	2.31 (2.04–2.58)	2.79 (2.29–3.28)	5.33 (3.86–6.81)
13	2.70 (2.28–3.12)	3.23 (2.77–3.70)	2.31 (1.95–2.66)	3.23 (2.79–3.67)	4.72 (4.18–5.26)
14	3.76 (2.80–4.73)	3.12 (2.62–3.63)	2.45 (2.22–2.68)	2.81 (2.37–3.25)	8.10 (6.25–9.94)
15	2.98 (2.44–3.52)	2.59 (2.13–3.04)	2.22 (2.02–2.43)	3.38 (2.66–4.11)	4.93 (3.58–6.29)
16	2.57 (2.26–2.89)	2.80 (2.53–3.08)	2.25 (2.10–2.39)	2.89 (2.34–3.44)	4.23 (3.23–5.24)
17	2.66 (2.38–2.94)	2.66 (2.15–3.16)	2.20 (2.02–2.38)	2.85 (2.44–3.25)	5.22 (3.77–6.67)
18	2.64 (2.13–3.14)	2.72 (2.49–2.96)	2.19 (1.95–2.44)	2.88 (2.44–3.32)	5.26 (4.12–6.39)
19	3.04 (2.59–3.48)	2.86 (2.50–3.22)	2.32 (1.92–2.71)	3.66 (3.09–4.24)	4.29 (3.71–4.87)

number of factors, including sex, race, degree of adiposity, and pubertal stage (1), we found that no other factor considered, i.e., age, sex, or race/ethnicity, was nearly as influential on HOMA-IR status as weight status, specifically obesity. Our results are consistent with previous studies that demonstrated that obesity is one of the most important risk factors for insulin resistance (28,29).

Girls and children from minority groups have been shown to have a higher propensity toward insulin resistance (30–33). In our study, girls had a higher mean HOMA-IR than boys after accounting for weight, age, and race/ethnicity. Similarly, after adjustment for sex, age, and weight status, we found higher mean HOMA-IR values for Mexican-American adolescents, but we did not find significant differences in HOMA-IR between black and white adolescents. This lack of a difference between black and white children is in contrast to the results of previous studies (31,32) using clamps or FSIVGTT. One study (12) compared measures of insulin resistance by clamp and fasting methods in a small sample of black and white prepubertal nonobese children ($n = 44$). Although statistical differences in insulin resistance between black and white children were detected using clamp measures, differences in HOMA-IR only approached statistical significance ($P = 0.095$). It was postulated that this was due to the small sample size using a less sensitive measure of insulin resistance (12). Despite the large sample size in our study, we did not find differences in HOMA-IR levels between black and white children. We speculate that the lack of racial differences noted in our study may be due to the fact that HOMA-IR is measured in the fasting state, whereas clamp studies evaluate the insulin-stimulated state.

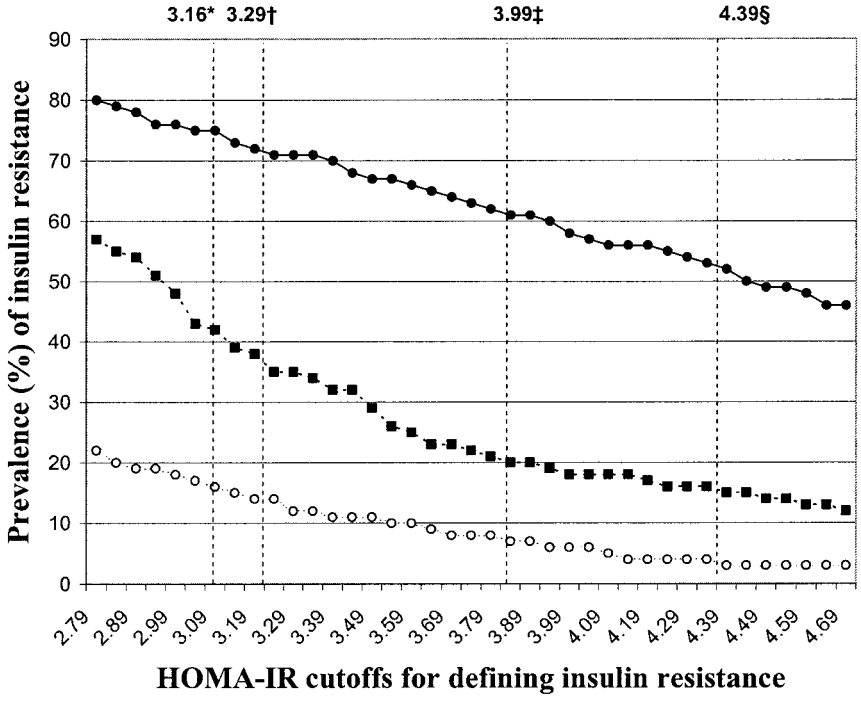

Figure 1—*Prevalence of insulin resistance according to various HOMA-IR cutoffs. *HOMA-IR threshold based on receiver-operator curve analysis (11). †HOMA-IR threshold defined by the upper quartile of insulin resistance for all adolescents in this study. ‡HOMA-IR threshold based on adult studies (27). §HOMA-IR threshold defined by the upper 2.5 percentile based on non–log-transformed HOMA-IR for normal-weight adolescents with NFG in this study. ○, normal weight; ■, overweight; ●, obese.*

We were unable to assess the impact of puberty on HOMA-IR levels. Puberty is associated with temporary increases in insulin resistance (30,34,35) with a peak reduction in insulin sensitivity of 25–30% by Tanner stage 3 and complete recovery by pubertal completion (36). We did examine HOMA-IR levels for each year of adolescence (12–19 years), a period during which most children would experience puberty. The earlier peak in HOMA-IR levels that we saw in girls compared with boys may reflect the effect of puberty on insulin resistance, as girls experience puberty at an earlier age than boys. Prevailing wisdom would suggest that HOMA-IR values performed during puberty are difficult to interpret because of the effects of puberty on insulin resistance. We saw substantial variability by age in HOMA-IR for obese children but not for normal- or overweight children. Therefore, we speculate that HOMA-IR values during puberty may still accurately reflect the degree of insulin resistance, at least for normal- and overweight children.

Currently, there is no strict definition for insulin resistance in children or adolescents (37). We present prevalence estimates of insulin resistance based on different definitions (11,27). Regardless of the defined threshold, a significantly higher proportion of overweight and obese children had insulin resistance. A

HOMA-IR threshold of 2 SD above the mean for normal-weight adolescents with NFG (>4.39) may represent a reasonable definition of insulin resistance, as it was derived through a standard method for determining abnormal values within a population, and as a conservative estimate it results in the lowest proportion of normal-weight children classified as having insulin resistance.

Given that insulin resistance is thought to represent an initial step in the pathogenesis of type 2 diabetes (1,12), the high prevalence estimates of insulin resistance in obese children foreshadows a concerning trend for the future burden of type 2 diabetes in U.S. children.

Limitations

Previous studies have demonstrated high correlations of HOMA-IR with more precise measures of insulin resistance derived from clamp studies or FSIVGTT (10,12). We acknowledge, however, that HOMA-IR is not as sensitive a method for determining insulin resistance compared with these other methods. Therefore, we may have somewhat underestimated the prevalence of insulin resistance in our study population. Furthermore, HOMA-IR is measured in the fasting state, whereas clamp studies evaluate insulin resistance in an insulin-stimulated state.

BMI is a surrogate measure of adiposity, which correlates with fat-free mass and total body fat (38). We did not account for differences in body fat distribution, which may differ among races and impact insulin sensitivity (39). Although studies have demonstrated that waist circumference is associated with abdominal fat and insulin resistance in children (40), we did not include waist circumference in this analysis as there are no defined standard categories of risk for waist circumference in children as with BMI (41).

We created a definition of insulin resistance based on normal-weight children with NFG; however, glucose tolerance tests were not performed. Therefore, it is possible that some children in the normal-weight group may have had impaired glucose tolerance, which would limit the definition of "normal" in these patients.

Finally, NHANES used a single uniform assay on the subjects' specimens, allowing for comparison of HOMA-IR levels among a diverse representative population of U.S. children. However, there is concern regarding uncertain comparability of insulin levels among various laboratories (42).

In this population-based sample of adolescents, after accounting for race, sex, and age, weight status was the most important determinant of insulin resistance as measured by HOMA-IR. A majority of obese adolescents in the U.S. have insulin resistance. Strategies for weight reduction and prevention of obesity in children are likely necessary to prevent the future development of type 2 diabetes among children and young adults in the U.S.

Acknowledgments— J.M.L. was supported by a T32HD 07534-05 National Institutes of Health/National Institute of Child Health and Human Development Pediatric Health Services Research Training Grant.

This work was presented as an abstract at the American Diabetes Association's Scientific Sessions in June 2006.

We thank Ram Menon for his thoughtful contributions to the manuscript.

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