Prevalence of Pre-Diabetes and Its Association With Clustering of Cardiometabolic Risk Factors and Hyperinsulinemia Among U.S. Adolescents

National Health and Nutrition Examination Survey 2005–2006

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OBJECTIVE — Impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are considered to constitute "pre-diabetes." We estimated the prevalence of IFG, IGT, and pre-diabetes among U.S. adolescents using data from a nationally representative sample.

RESEARCH DESIGN AND METHODS — We analyzed data from participants aged 12–19 years in the National Health and Nutrition Examination Survey 2005–2006. We used fasting plasma glucose and 2-h glucose during an oral glucose tolerance test to assess the prevalence of IFG, IGT, and pre-diabetes and used the log-binomial model to estimate the prevalence ratios (PRs) and 95% CIs.

RESULTS — The unadjusted prevalences of IFG, IGT, and pre-diabetes were 13.1, 3.4, and 16.1%, respectively. Boys had a 2.4-fold higher prevalence of pre-diabetes than girls (95% CI 1.3–4.3). Non-Hispanic blacks had a lower rate than non-Hispanic whites (PR 0.6, 95% CI 0.4–0.9). Adolescents aged 16–19 years had a lower rate than those aged 12–15 years (0.6, 0.4–0.9). Overweight adolescents had a 2.6-fold higher rate than those with normal weight (1.3–5.1). Adolescents with two or more cardiometabolic risk factors had a 2.7-fold higher rate than those with none (1.5–4.8). Adolescents with hyperinsulinemia had a fourfold higher prevalence (2.2–7.4) than those without. Neither overweight nor number of cardiometabolic risk factors was significantly associated with pre-diabetes after adjustment for hyperinsulinemia.

CONCLUSIONS — Pre-diabetes was highly prevalent among adolescents. Hyperinsulinemia was independently associated with pre-diabetes and may account for the association of overweight and clustering of cardiometabolic risk factors with pre-diabetes.

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Individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are at increased risk for diabetes and cardiovascular-related death (1,2). The state of abnormal glucose metabolism characterized as IFG and/or IGT has been referred to as "pre-diabetes" (3).

Previous studies of IGT among children and adolescents have been largely limited to those with obesity, a family history of diabetes, or multiple cardiometabolic risk factors. The prevalence estimates of IGT varied from 4 to 21% in previous studies (4–7). Although IGT prevalence estimates among overweight adolescents is helpful in understanding the absolute health risk associated with IGT in this special population, the relative health burden of IGT among overweight adolescents compared with that among adolescents of normal weight has not been established. In a few school-based studies, the prevalence of IGT is estimated to range from 0.3 to 2.3%, and the prevalence of IFG is estimated to vary from 6.7 to 40.5% (8–10). However, because the samples for these studies were selected from students at a small number of schools in narrow geographic areas, these results may not be generalizable to the entire U.S. adolescent population.

Estimates based on National Health and Nutrition Examination Survey (NHANES) data indicated that the prevalence of IFG among U.S. adolescents aged 12–19 years was ~7% during 1999–2000 (11). However, NHANES did not collect IGT data on U.S. adolescents before 2005–2006. To estimate the prevalence of IGT, IFG, and pre-diabetes among U.S. adolescents aged 12–19 years and to assess selected correlates of these dysglycemic states, we thus examined the NHANES 2005–2006 data.

RESEARCH DESIGN AND METHODS

— The NHANES 2005–2006 sample was drawn from the noninstitutionalized civilian U.S. population, and a multistage, stratified sampling design was used to recruit survey participants (12,13). NHANES 2005–2006 includes oversamples of low-income individuals, adolescents aged 12–19 years, African Americans, and Mexican Americans. A total of 2,689 adolescents aged 12–19 years (population size 33,448,181) were selected, 2,288 were interviewed (response rate 85.0%; interview sample), and 2,207 were examined (response rate, 82.0%). There were 1,041 boys and nonpregnant girls aged 12–19 years randomly assigned to a morning session. After having fasted for 8–24 h, 871 (83.7%) were tested for fasting plasma glucose (FPG subsample). Of those in the FPG subsample, 781 (89.7%)

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were tested for an oral glucose tolerance test (OGTT subsample).

Details of NHANES laboratory procedures have been described elsewhere (12,13). In brief, blood specimens were frozen and stored at −70°C until analysis. The plasma glucose concentration was determined with a hexokinase method on a Roche/Hitachi 911 analyzer at the Fairview Medical Center Laboratory of the University of Minnesota. After an initial blood sample was drawn for FPG testing, participants were asked to drink a calibrated dose of Trutol (75 g glucose). Two hours (±15 min) later, a second plasma sample was drawn and tested for postload glucose concentrations. To maintain consistency with previous NHANES surveys, we converted glucose concentrations as follows: glucose (Cobas Mira) = 0.9835 × glucose (Hitachi 911) (13).

HDL cholesterol was measured directly in serum with Roche/Boehringer-Mannheim diagnostics. Serum triglyceride was determined in a sequence of three coupled enzymatic steps involving glycerol kinase, glycerophosphate oxidase, and horseradish peroxidase. Serum insulin was measured with the Merocodia Insulin ELISA (13). Homeostasis model assessment (HOMA = [glucose (millimoles per liter) × insulin (microunits per milliliter)]/22.5) was used as a measure of insulin resistance (IR) (14). Adolescents with fasting insulin or HOMA >75th percentile cutoff value were considered to have hyperinsulinemia or HOMA-IR.

Participants' BMI (weight in kilograms divided by the square of height in meters) was calculated from their measured weight and height. The BMI percentile was used to categorize participants' weight status as normal (<85th percentile), at risk of becoming overweight (85th–94th percentile), and overweight (≥95th percentile) (15). Participants' waist circumference was measured at the level of the iliac crest on the midaxillary line at minimal respiration to the nearest 0.1 cm (13). The mean blood pressure was calculated as the average of the second and third readings for those who had three measurements, the second reading for those who had two measurements, and the only reading for those who had one measurement (13).

Definitions of IFG, IGT, and pre-diabetes

An adolescent is considered to have a provisional diagnosis of diabetes if his or her FPG is ≥7.0 mmol/l (126 mg/dl) or 2-h glucose is ≥11.1 mmol/l (200 mg/dl). IFG was defined as having FPG ≥5.6 mmol/l (100 mg/dl) but <7.0 mmol/l (126 mg/dl). IGT was defined as having 2-h glucose ≥7.8 mmol/l (140 mg/dl) but <11.1 mmol/l (200 mg/dl). Pre-diabetes was defined as having IFG and/or IGT (3).

Table 1—*Unadjusted prevalence of IFG, IGT, and pre-diabetes among nondiabetic U.S. adolescents aged 12–19 years, NHANES 2005–2006*

	n	IFG	IGT	Pre-diabetes
n		99	23	117
All*	777	13.1 ± 1.9	3.4 ± 1.0	16.1 ± 2.4
Sex				
Female (nonpregnant only)	381	5.9 ± 1.6	4.4 ± 2.0†	9.5 ± 3.0†
Male	396	20.0 ± 2.3	2.5 ± 1.2†	22.4 ± 2.2
Race/ethnicity				
Non-Hispanic white	189	14.1 ± 2.4	3.7 ± 1.3†	17.2 ± 2.8
Non-Hispanic black	257	9.7 ± 1.6	0.9 ± 0.6†	10.3 ± 1.6
Mexican American	277	14.3 ± 2.7	3.5 ± 1.0	16.9 ± 2.8
Age (years)				
12–15	388	15.8 ± 3.2	5.7 ± 1.9†	20.6 ± 3.6
16–19	389	10.6 ± 2.0	1.3 ± 0.9†	11.8 ± 2.1
Weight status				
Normal	478	9.9 ± 2.1	1.6 ± 0.9†	11.6 ± 1.9
At risk for overweight‡	134	14.9 ± 5.7†	3.6 ± 1.8†	18.3 ± 5.6†
Overweight§	165	22.7 ± 7.5†	9.5 ± 3.2†	30.0 ± 7.5
Hyperinsulinemia‖				
No	534	7.9 ± 1.6	1.2 ± 0.7†	9.2 ± 1.8
Yes	236	28.5 ± 5.3	9.9 ± 3.2†	36.7 ± 6.6
HOMA-IR				
No	533	7.5 ± 1.6	1.7 ± 0.8†	9.1 ± 1.6
Yes	237	30.2 ± 5.8	8.7 ± 2.7†	37.1 ± 6.4

Data are mean percentages ± SE. *Including non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and other race/ethnicity. †Does not meet the standard of statistical reliability and precision (i.e., relative SE >30%). ‡Defined as 85th ≤ BMI <95th percentile. Defined as a BMI ≥95th percentile. ‖Defined as >75th percentile of fasting insulin (82.5 pmol/l or 13.8 μU/ml) by the Mercodia method. To convert fasting insulin (FI) between the Mercodia and the Tosoh methods, use the following formula: FI (Tosoh) = 1.0526 × FI (Mercodia) − 1.5674. To convert picomoles per liter to microunits per milliliter, divide by 6.

Definitions of cardiometabolic risk factors

The International Federation of Diabetes criteria were used to determine whether participants had any of the four conditions that are part of the metabolic syndrome (i.e., central obesity, high triglycerides, low HDL cholesterol, and high blood pressure) (16,17). For all adolescents, a high triglyceride level was defined as ≥1.7 mmol/l (150 mg/dl), and high blood pressure was defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥85 mmHg (16,17). For adolescents aged 12–15 years, central obesity was defined as a waist circumference ≥90th percentile, and low HDL cholesterol was defined as <1.03 mmol/l (40 mg/dl). For adolescents aged 16–19 years, the International Federation of Diabetes sex- and race/ethnicity-specific cutoff values of waist circumference (i.e., white males ≥94 cm, African American males ≥94 cm, Mexican-American males ≥90 cm, white females ≥80 cm, African American females ≥80 cm, and Mexican-American females ≥80 cm) were used to define central obesity. Sex-specific cutoff values of HDL cholesterol (i.e., <1.03 mmol/l [40 mg/dl] in males and <1.29 mmol/l [50 mg/dl] in females) were used to define low HDL cholesterol (16). Current use of prescribed antihypertensive medicines for the treatment of previously diagnosed hypertension was considered to be high blood pressure.

Statistical analysis

We calculated the unadjusted prevalence of IFG, IGT, and pre-diabetes by sex, race/ethnicity, age, BMI categories, number of cardiometabolic risk factors, hyperinsulinemia, and HOMA-IR. Appropriate sampling weights of the interview sample and FPG or OGTT subsample were used to obtain the population prevalence estimates for U.S. adolescents aged 12–19

years. In addition, we estimated the unadjusted and adjusted prevalence ratios (PRs) and their 95% CIs using a multivariable log-binomial model (18). We performed all analyses using SAS (version 9.1; SAS Institute, Cary, NC) and SUDAAN software (release 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the complex sampling design. We considered results with a two-tailed $P \leq 0.05$ to be statistically significant.

RESULTS

Demographic characteristics

In the interview sample, there were 1,133 boys and 1,155 girls. There were 578 non-Hispanic whites, 782 non-Hispanic blacks, 747 Mexican Americans, and 181 adolescents with other race/ethnicity. The mean age was 15.5 years. Demographic characteristics in the FPG and OGTT subsamples were similar to those of the interview sample.

Prevalence of diagnosed diabetes and pre-diabetes

There were seven adolescents who reported having diagnosed diabetes (weighted prevalence ± SE 0.23 ± 0.14%), of whom two used insulin, two used oral hypoglycemic agents, and three did not use either insulin or hypoglycemic agents. Thirty adolescents reported having either diagnosed borderline diabetes or pre-diabetes (weighted prevalence 0.91 ± 0.24%).

Prevalence of diabetes based on FPG and 2-h glucose

There were six adolescents who met the FPG diabetes criteria (weighted prevalence 0.49 ± 0.33%). Of these six, four reported having diabetes and two did not (undiagnosed diabetes 0.06 ± 0.04%). No adolescents met the 2-h glucose diabetes criteria.

Prevalence of IFG, IGT, and pre-diabetes

To estimate the prevalence of IFG, IGT, and pre-diabetes, we further excluded two participants with diagnosed diabetes and two participants with an FPG ≥7.0 mmol/l. The unadjusted IFG, IGT, and pre-diabetes prevalence rates are shown in Table 1.

Of the 777 adolescents, 660 (population-weighted proportion, 83.9%) had neither IFG nor IGT, 94 (12.6%) had only IFG (isolated IFG), 18 (3.0%) had only IGT (isolated IGT), and 5 (0.5%) had both IFG and IGT. The weighted proportions of isolated IFG, isolated IGT, and both IFG and IGT were 78.7, 18.4, and 2.9%, respectively.

The prevalence of IFG, IGT, and pre-diabetes was each positively associated with the number of cardiometabolic risk factors that participants had (Fig. 1*A*). Overweight adolescents with hyperinsulinemia had a higher prevalence of IFG ($P < 0.05$), IGT ($P < 0.05$), and pre-diabetes ($P < 0.05$) than those of normal weight with normal insulin (Fig. 1*B*).

The unadjusted prevalence of pre-diabetes was higher among boys than among girls ($P < 0.001$), lower among non-Hispanic blacks than among non-Hispanic whites ($P < 0.05$) and Mexican Americans ($P < 0.05$; data not shown), lower among adolescents aged 16–19 than among those aged 12–15 ($P < 0.05$), and 2.6 times higher among adolescents who were overweight than among those of normal weight ($P < 0.05$) (Table 2, model 1). The prevalence ratios between adolescents with and without pre-

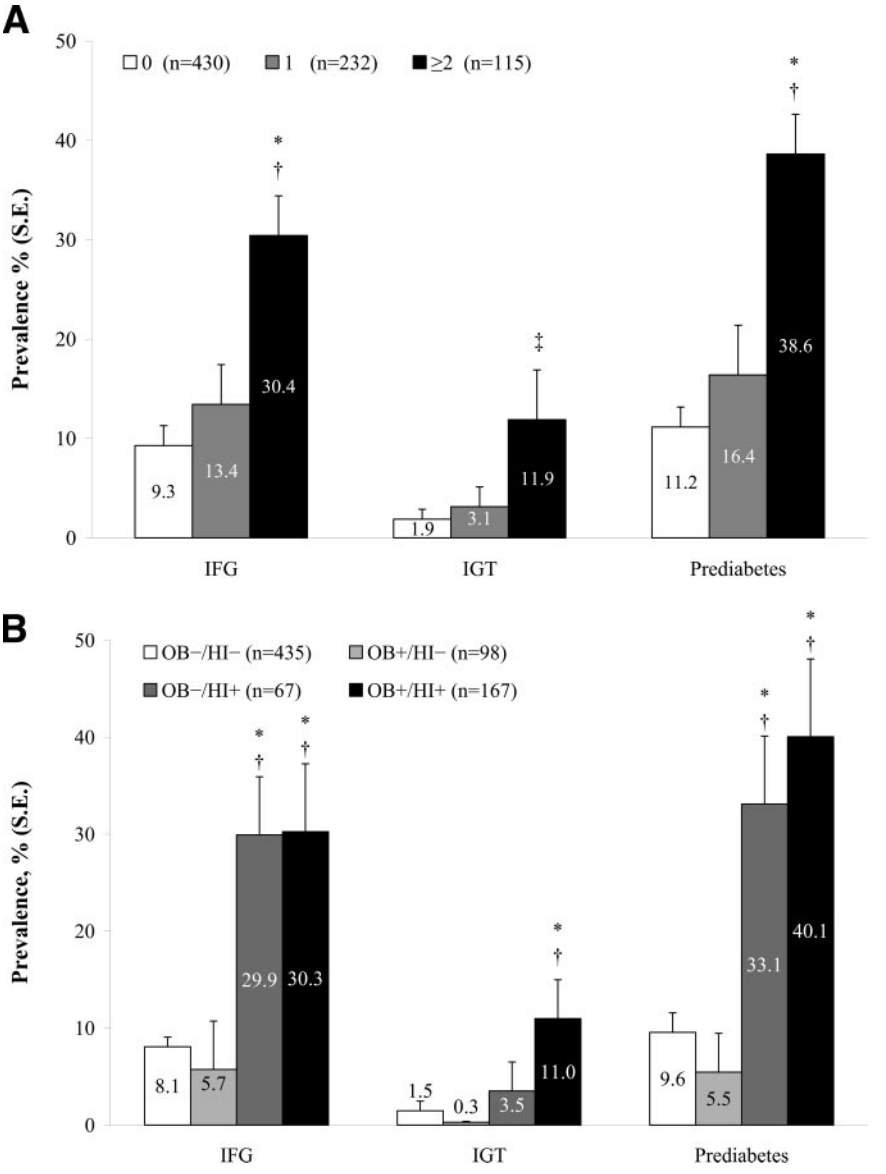

Figure 1—*Prevalence of IFG, IGT, and pre-diabetes according to the number of cardiometabolic risk factors* (A) (*P < 0.05, compared with the 0 group; †P < 0.01, compared with the 1 group; ‡P < 0.10, compared with the 0 group), and a combination of central obesity and hyperinsulinemia* (B) (*P < 0.05, compared with the OB−/HI− group; †P < 0.05 compared with the OB+/HI− group). OB, central obesity; HI, hyperinsulinemia, defined as >75th percentile of fasting insulin (82.5 pmol/l or 13.75 μU/ml) by the Mercodia method. To convert fasting insulin (FI) between the Mercodia and the Tosoh methods, see footnote ‖ to Table 1.*

Table 2—*Unadjusted and adjusted prevalence ratios for pre-diabetes among nondiabetic U.S. adolescents aged 12–19 years, NHANES 2005–2006*

	n	Model 1	Model 2	Model 3
Sex				
Female (nonpregnant only)	381	1.0 (—)	1.0 (—)	1.0 (—)
Male	396	2.4 (1.3–4.3)	3.0 (1.9–4.8)	2.9 (1.8–4.6)
Race/ethnicity				
Non-Hispanic white	189	1.0 (—)	1.0 (—)	1.0 (—)
Non-Hispanic black	257	0.6 (0.4–0.9)	0.5 (0.4–0.8)	0.5 (0.4–0.8)
Mexican American	277	1.0 (0.6–1.6)	0.8 (0.5–1.2)	0.7 (0.5–1.0)
Age (years)				
12–15	388	1.0 (—)	1.0 (—)	1.0 (—)
16–19	389	0.6 (0.4–0.9)	0.5 (0.3–0.9)	0.6 (0.3–1.0)
Weight status				
Normal	478	1.0 (—)	1.0 (—)	1.0 (—)
At risk for overweight*	134	1.6 (0.8–3.0)	1.4 (0.7–3.0)	1.2 (0.7–2.1)
Overweight†	165	2.6 (1.3–5.1)	2.1 (1.1–3.8)	0.9 (0.6–1.5)
Number of cardiometabolic risk factors‡				
0	430	1.0 (—)	1.0 (—)	1.0 (—)
1	232	1.2 (0.5–2.5)	1.1 (0.6–2.3)	0.9 (0.5–1.6)
≥2	115	2.7 (1.4–5.2)	2.2 (1.2–3.9)	1.5 (0.8–2.6)
Hyperinsulinemia§				
≤75th percentile	534	1.0 (—)	—	1.0 (—)
>75th percentile	236	4.0 (2.2–7.4)	—	4.1 (2.3–7.2)

Data are prevalence ratios (95% CI). Model 1 included each single variable only. Model 2 included sex, race/ethnicity, age, weight status, and number of cardiometabolic risk factors. Model 3 included sex, race/ethnicity, age, weight status, number of cardiometabolic risk factors, and hyperinsulinemia. *Defined as 85th ≤ BMI < 95th percentile. †Defined as BMI ≥95th percentile. ‡The cardiometabolic risk factors consisted of central obesity, high blood pressure, low HDL cholesterol, and high triglycerides in accordance with the definition proposed by the International Federation of Diabetes (16,17). §Defined as >75th percentile of fasting insulin (82.5 pmol/l or 13.8 μU/ml) by the Mercodia method. To convert fasting insulin between the Mercodia and the Tosoh methods, see footnote ‖ to Table 1.

diabetes altered slightly but remained statistically significant after adjustments for sex, race/ethnicity, age, weight status, and number of cardiometabolic risk factors (Table 2, model 2).

Adolescents who had two or more of the four cardiometabolic risk factors had a 2.7-fold higher unadjusted rate of pre-diabetes than those with no risk factors ($P < 0.001$) (Table 2, model 1) and a 2.3-fold higher prevalence than those with one risk factor (95% CI 1.2–4.4; $P < 0.01$; data not shown). Moreover, the unadjusted prevalence of pre-diabetes was four times higher among adolescents with hyperinsulinemia than among those with fasting insulin ≤75th percentile ($P < 0.01$) (Table 2, model 1). However, age, weight status, and number of cardiometabolic risk factors were no longer significantly associated with pre-diabetes prevalence after adjustment for hyperinsulinemia (Table 2, model 3).

Adolescents with IFG, IGT, or pre-diabetes had a higher geometric mean of fasting insulin (Fig. 2*A*) and HOMA (Fig. 2*B*) than those without these conditions (all $P < 0.01$). The mean ± SE fasting insulin value of adolescents with isolated IGT (101.0 ± 15.4 pmol/l) and that of those with isolated IFG (94.4 ± 8.7 pmol/l) were similar ($P = 0.76$), and both were significantly higher than that of adolescents with neither IGT nor IFG (53.5 ± 1.6 pmol/l) (all $P < 0.01$; data not shown).

CONCLUSIONS — Using the most recent NHANES data, we estimated that the national population-based prevalence rates of IFG, IGT, and pre-diabetes among U.S. adolescents aged 12–19 years were 13.1, 3.4, and 16.1%, respectively. IFG accounted for nearly 80% of adolescents with pre-diabetes. Pre-diabetes risk was positively associated with being male and having hyperinsulinemia and negatively associated with being a non-Hispanic black. Moreover, hyperinsulinemia appeared to account for the association of weight status and clustering of cardiovascular risk factors with pre-diabetes.

The prevalence of IGT has been found to be high among adolescents with obesity (21%) (5) or those with a positive family history of type 2 diabetes (25%) (6) and in particular among those with both obesity and a positive family history of type 2 diabetes (35%) (7). In contrast, several school-based studies have reported a relatively low prevalence of IGT. In Poland, the prevalence of IGT was found to be 0.3% among all children and adolescents aged 8–19 years but 7.1% among those who were obese (8). The results of the Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) indicated that the prevalence of IGT was 2.3% among all eighth graders in four middle schools of Southern California, Texas, and North Carolina but 4.1% among those who were overweight (9). In the Princeton School District of Cincinnati (10), IGT was detected among only 0.5% of 5th to 12th graders. It is possible that sampling and geographic variations may account for these low prevalences. To the best of our knowledge, our study is the first report on the prevalence estimate of IGT using a nationally representative sample of U.S. adolescents. Our IGT prevalence estimates among all adolescents (3.4%) and among overweight adolescents (9.5%) were lower than the rates reported in clinic-based studies but higher than the rates reported in school-based studies.

Our estimated IFG prevalence of 13.1% among U.S. adolescents in 2005–2006 was 87.1% higher than the 7% estimated from NHANES data in 1999–2000 (11). Rapid increases in the prevalence of central obesity (19) among adolescents may be a factor in the increased prevalence of IFG. Our results indicated that overweight adolescents had a nearly two-fold higher prevalence of IFG than did those with normal weight.

It is noteworthy that adolescents with two or more of the four cardiometabolic risk factors (i.e., central obesity, high triglyceride, low HDL cholesterol, and elevated blood pressure) had a significantly higher prevalence of pre-diabetes than those with zero or one risk factor. These findings, which were in agreement with those from previous studies (6,7), have several clinical implications. The presence of two or more cardiometabolic risk factors among adolescents may be an indication that their pre-diabetes status should be assessed. Because pre-diabetes is an intermediate stage in the development of type 2 diabetes and has been shown to be reversible through pharmacological and lifestyle interventions (20),

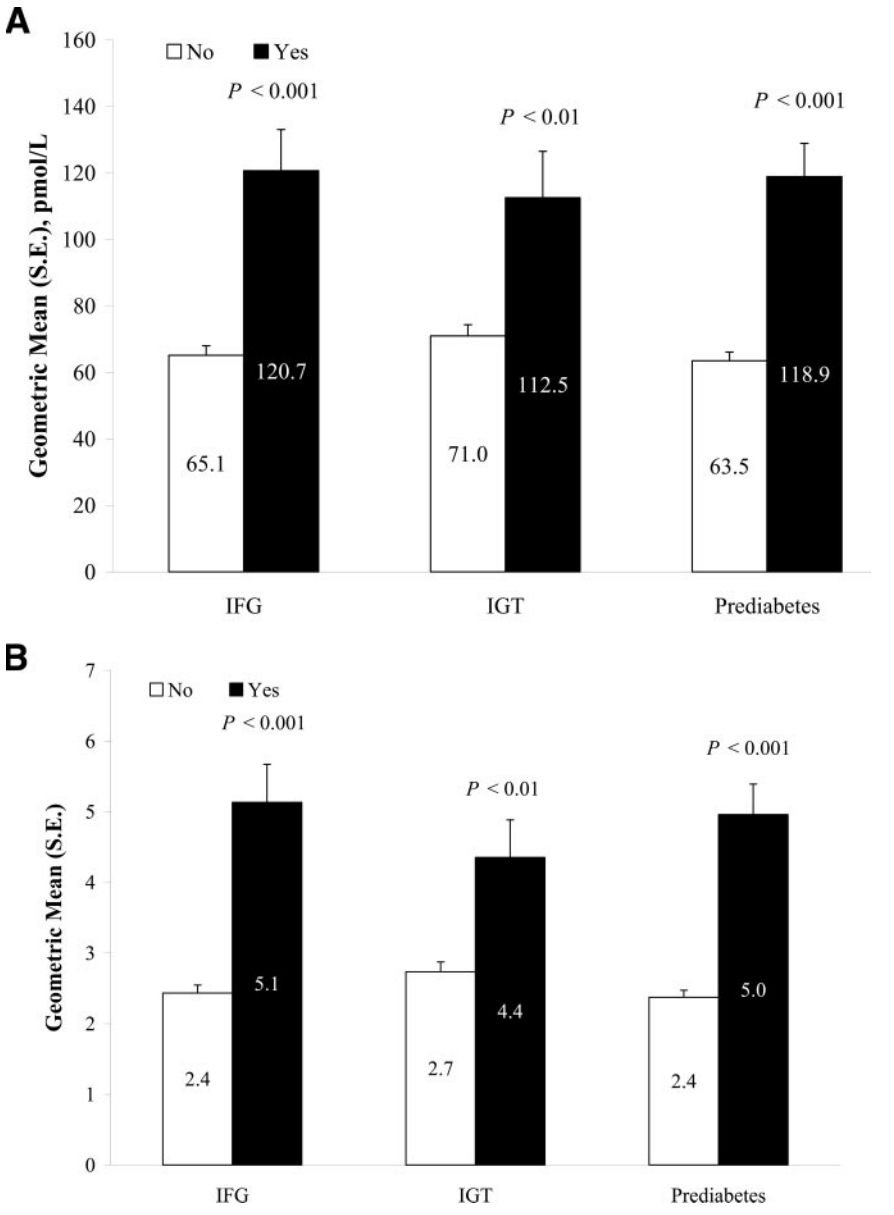

Figure 2—*Geometric means and 95% CIs of fasting insulin (picomoles per liter, Mercodia method)* (A) *and HOMA* (B) *among U.S. adolescents, ages 12–19, by IFG, IGT, and pre-diabetes status* (n = 777).

early detection and appropriate management of pre-diabetes among adolescents could effectively prevent or delay their development of type 2 diabetes in later life.

As previous studies have shown (5,6), we found that adolescents with pre-diabetes had significantly higher fasting insulin levels than those without pre-diabetes. In one previous study, insulin resistance was found to be the best predictor of 2-h plasma glucose in an OGTT among obese adolescents (5). It has been proposed that insulin resistance is a major underlying cause of type 2 diabetes (21), and intramyocellular and intra-abdominal lipid accumulation is highly associated with the development of insulin resistance (22). Our results indicated that hyperinsulinemia or insulin resistance may play an important role in the association of obesity and clustering of cardiometabolic risk factors with pre-diabetes. The prevalence of hyperinsulinemia has increased by ~35% in the past decade among U.S. adults (23). Therefore, early identification and effective treatment of insulin resistance could prevent or delay the occurrence of pre-diabetes and diabetes among both adolescents and adults (24).

Similar to the finding of a previous study (10), our results demonstrated that only 2.9% of adolescents with glucose intolerance had both IFG and IGT. IFG and IGT may identify different populations at risk of developing diabetes. It has been proposed that IFG and IGT represent distinct metabolic abnormalities with different etiological mechanisms, with IFG being caused by impaired basal insulin secretion and IGT being caused primarily by peripheral insulin resistance (25). Despite these etiological differences, however, IFG and IGT have both been associated with an increased risk of developing diabetes and subsequent cardiovascular disease (1–3), and, as we showed, both are strongly associated with obesity and clustering of cardiometabolic risk factors before adjustment for hyperinsulinemia. Therefore, from a public health point of view, it seems tenable to use the term "pre-diabetes" to describe the condition of IFG and/or IGT and to identify adolescents at increased risk for diabetes in later life.

Our results are subject to two limitations. First, the cross-sectional design of the NHANES study precluded a causal inference among obesity, clustering of cardiometabolic risk factors, insulin resistance, and pre-diabetes. Future studies with a longitudinal design are warranted to identify the temporal sequence among these variables. Second, because of the low prevalence of IGT, we were unable to conduct separate analyses of factors associated with IGT. Therefore, our results for pre-diabetes may be influenced mainly by IFG. However, because our study was focused on pre-diabetes prevalence estimates rather than its predictors, interpretation of our results may not be affected.

In summary, the high prevalence of pre-diabetes among adolescents has raised public health concerns. Because adolescents with pre-diabetes usually have no apparent clinical symptoms, great efforts may be needed to identify them early and to intervene against the root causes of insulin resistance such as overweight, physical inactivity, and unhealthy diet in pediatric primary care and through public health services.

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