# The Metabolic Syndrome as Predictor of Type 2 Diabetes

## The San Antonio Heart Study

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**OBJECTIVE** — The oral glucose tolerance test identifies high-risk subjects for diabetes, but it is costly and inconvenient. To find better predictors of type 2 diabetes, we evaluated two different definitions of the metabolic syndrome because insulin resistance, which is commonly associated with this clustering of metabolic factors, frequently precedes the onset of type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — We compared the ability of the National Cholesterol Education Program (NCEP) definition, a modified version of the 1999 World Health Organization (WHO) definition that excludes the 2-h glucose requirement, and impaired glucose tolerance (IGT) to predict incident type 2 diabetes. In the San Antonio Heart Study, 1,734 participants completed a 7- to 8-year follow-up examination.

**RESULTS** — IGT and the NCEP definition had higher sensitivity than the modified WHO definition (51.9, 52.8, and 42.8%, respectively). IGT had a higher positive predictive value than the NCEP and modified WHO definitions (43.0, 30.8, and 30.4%, respectively). The combination of the IGT and NCEP definitions increased the sensitivity to 70.8% with an acceptable positive predictive value of 29.7%. Risk for incidence of type 2 diabetes using the NCEP definition was independent of other risk factors, including IGT and fasting insulin (odds ratio 3.30, 95% CI 2.27–4.80). The NCEP definition performed better with fasting glucose ≥5.4 mmol/l (sensitivity 62.0% and positive predictive value 30.9%).

**CONCLUSIONS** — The metabolic syndrome predicts diabetes independently of other factors. However, the NCEP definition performs better than the modified 1999 WHO definition. Lowering the fasting glucose cutoff to 5.4 mmol/l improves the prediction of diabetes by the metabolic syndrome.

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The metabolic syndrome has been shown to predict cardiovascular and coronary heart disease mortality in two Finnish studies (1,2). The National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (3) has proposed a definition that only requires readily available clinical variables. On the other hand, the 1999 World Health Organization (WHO) definition requires the presence of diabetes, impaired glucose tolerance (IGT), or insulin resistance and two other risk factors (4). IGT requires an oral glucose tolerance test (OGTT), and precise measurement of insulin resistance requires an insulin clamp study.

The OGTT is the standard method for identifying subjects at increased risk for developing type 2 diabetes in clinical research. However, OGTT is not widely used in clinical practice because it is inconvenient and costly. Identifying subjects at risk for diabetes has become more relevant because of the positive results seen with lifestyle modification and medication in the prevention (or delay) of type 2 diabetes (5–9).

In seeking better predictors of type 2 diabetes, we evaluated two different definitions of the metabolic syndrome because insulin resistance, which is commonly associated with this clustering of metabolic factors, frequently precedes the onset of type 2 diabetes. We compared the ability of the NCEP definition, a modified version of the 1999 WHO definition of the metabolic syndrome, and IGT to predict the incidence of type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Subjects

The San Antonio Heart Study (SAHS) is a population-based, epidemiological study of type 2 diabetes and cardiovascular disease (initial response rate 65.3%). A total of 2,941 Mexican Americans and non-Hispanic whites aged 25–68 years were enrolled in phase 2 (10,11). We excluded participants in phase 1 (waist circumference was not measured) and those in phase 2 with diabetes at baseline (baseline prevalence of type 2 diabetes 10.6%). From a total of 2,569 eligible participants, 1,734 subjects completed a 7- to 8-year follow-up examination. Survey protocols at baseline and follow-up were identical and were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave written informed consent.

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**Abbreviations:** IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; ROC, receiver-operating characteristic; SAHS, San Antonio Heart Study; WHO, World Health Organization.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**See accompanying editorial, p. 3180.**

**Table 1—*Age- and sex-adjusted baseline characteristics by incident type 2 diabetes at follow-up***

| | No diabetes | Incident type 2 diabetes | *P* |
|---|---|---|---|
| *n* | 1,539 | 195 | — |
| Age (years)* | 42.7 ± 0.27 | 47.7 ± 0.77 | <0.0001 |
| Male (%)* | 42.8 | 39.0 | 0.363 |
| Mexican Americans (%)* | 64.1 | 80.5 | <0.0001 |
| Family history of diabetes (%)* | 30.3 | 45.6 | <0.0001 |
| BMI (kg/m$^2$) | 27.2 ± 0.13 | 31.3 ± 0.38 | <0.0001 |
| Waist circumference (cm) | | | |
| Men | 94.2 ± 0.40 | 101.2 ± 1.18 | <0.0001 |
| Women | 84.8 ± 0.46 | 96.4 ± 1.26 | <0.0001 |
| Fasting glucose (mmol/l) | 4.70 ± 0.01 | 5.27 ± 0.04 | <0.0001 |
| 2-h glucose (mmol/l) | 5.58 ± 0.04 | 7.61 ± 0.12 | <0.0001 |
| HDL cholesterol (mmol/l) | 1.24 ± 0.01 | 1.05 ± 0.02 | <0.0001 |
| Total cholesterol (mmol/l) | 5.07 ± 0.02 | 5.06 ± 0.07 | 0.828 |
| Triglycerides (mmol/l) | 1.50 ± 0.03 | 2.19 ± 0.08 | <0.0001 |
| SBP (mmHg) | 117.5 ± 0.35 | 123.6 ± 0.98 | <0.0001 |
| DBP (mmHg) | 71.5 ± 0.22 | 74.8 ± 0.64 | <0.0001 |
| Fasting insulin (μU/ml) | 12.2 ± 0.35 | 22.3 ± 0.98 | <0.0001 |
| IGT (%) | 7.4 | 44.9 | <0.0001 |
| IFG (%) | 1.0 | 7.4 | <0.0001 |
| NCEP definition (%) | 14.4 | 48.7 | <0.0001 |
| Modified WHO definition (%) | 12.5 | 41.3 | <0.0001 |

Data are means ± SE. *Not adjusted for age and sex. DBP, diastolic blood pressure; SBP, systolic blood pressure.

### Definition of variables and outcomes

Blood specimens were obtained after a 12- to 14-h fast for determination of plasma glucose and serum lipid and insulin concentrations. After a 75-g oral glucose load (Orangedex; Custom Laboratories, Baltimore, MD), blood specimens were collected 2 h later for plasma glucose determination. Plasma glucose and serum lipids were measured with an Abbott Bichromatic analyzer (South Pasadena, CA) (12). Serum insulin was measured by a radioimmunoassay (Diagnostic Products, Los Angeles, CA) with a relatively high degree of cross-reactivity with proinsulin (70–100%) (12). We used the 1999 WHO criteria for the diagnosis of type 2 diabetes, IGT, and impaired fasting glucose (IFG) at baseline and follow-up (4). Subjects on antihyperglycemic medications were considered to have diabetes.

The NCEP definition required at least three of the following: increased waist circumference (>102 cm in men and >88 cm in women) high triglycerides (≥1.7 mmol/l), low HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women), high blood pressure (≥130/85 mmHg or pharmacological treatment of hypertension), and fasting glucose (≥6.1 mmol/l) (3).

We used a modified version of the 1999 WHO definition for the metabolic syndrome (2,13,14). Microalbuminuria was excluded as a component of the metabolic syndrome because of its low prevalence in nondiabetic subjects (4%) and because the SAHS dataset did not collect information on albumin status (1). We also excluded IGT and insulin clamp–documented insulin resistance because of inconvenience, cost, and the lack of glucose uptake data in the SAHS (2,14). Thus, the modified WHO definition required fasting glucose ≥6.1 mmol/l (IFG) or hyperinsulinemia (fasting insulin in the top quartile of the nondiabetic population) plus at least two of the following: obesity (BMI ≥30 kg/m$^2$ or waist-to-hip ratio >0.9 in men or >0.85 in women), dyslipidemia (HDL cholesterol <0.9 in men and <1.0 mmol/l in women or triglycerides ≥1.7 mmol/l), or hypertension (≥140/90 mmHg or treated for hypertension) (2,14).

### Statistical methods

Statistical analyses were performed with the SAS statistical software system (Cary, NC). Continuous variables were evaluated by one-way ANCOVA. $\chi^2$ statistic with Yates correction for continuity was used for the analysis of dichotomous variables. Multiple logistic regression analysis assessed the diabetes risk of the metabolic syndrome independently of other covariates. Receiver-operating characteristic (ROC) curves were developed using the diabetes risks predicted for each person with the disorders of the metabolic syndrome or with the 2-h glucose value. We used the algorithm developed by DeLong et al. (15) for comparisons of areas under the ROC curves.

**RESULTS** — Baseline characteristics and prevalence of IGT, IFG, and the metabolic syndrome are shown after stratification by incident type 2 diabetes (Table 1). Fasting insulin in the upper quartile was present in 55.3% of subjects who fulfilled the NCEP definition and 96.4% of those who fulfilled the modified WHO definition.

Incident diabetes was diagnosed in 11.3% of the participants at the 7- to 8-year follow-up examination (13.7% in Mexican Americans and 6.4% in non-Hispanic whites). Incident diabetes was associated with age (particularly after 45 years of age), Mexican ethnicity, BMI, and fasting insulin but not with sex (Fig. 1*A–D*).

The sensitivity of predicting diabetes was higher for IGT and the NCEP definition than for the modified WHO definition (Table 2), but the positive predictive value was higher for IGT than for both definitions of the metabolic syndrome. Definitions of the metabolic syndrome were also evaluated in each ethnic group because of the different diabetic risk. In Mexican Americans, the NCEP definition had better sensitivity (51.6%) than the modified WHO definition (38.2%) but similar positive predictive value (33.6 and 32.1%, respectively). In non-Hispanic whites, those definitions were comparable (57.9 and 23.7% for the NCEP definition and 54.0 and 22.7% for the modified WHO definition, respectively).

Excluding IFG from the definitions of the metabolic syndrome made little difference in the sensitivity (from 52.8 to 49.2% for the NCEP definition and from 42.8 to 41.7% for the modified WHO definition) or specificity for predicting diabetes (from 86.4 to 87.2% for the NCEP definition and from 87.2 to 87.3% for the modified WHO definition). Due to the ar-

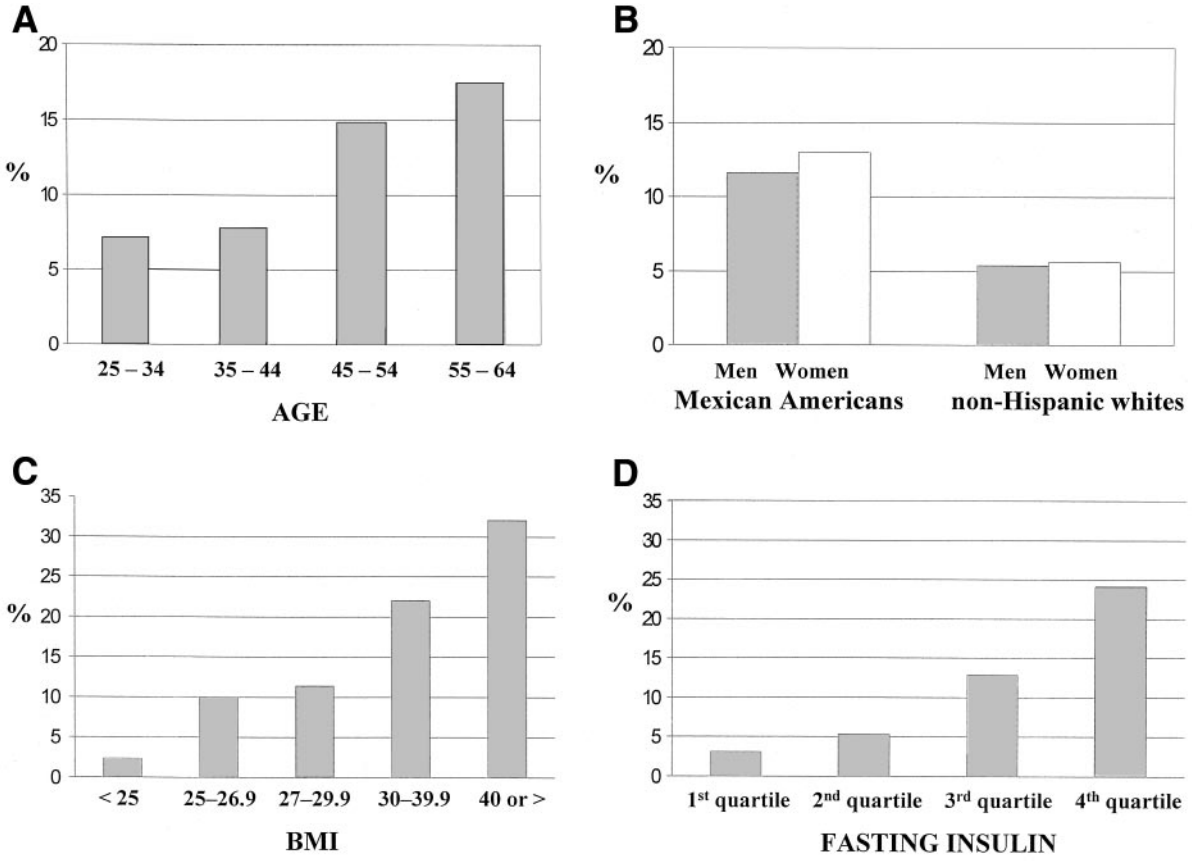


**Figure 1**—*Incident diabetes at the 7- to 8-year follow-up visit after stratification by age, sex, ethnicity, and BMI.* A: *Incident diabetes by age category* (P *for trend* <*0.0001*). B: *Age-adjusted incident diabetes by sex* (P = *0.352*) *and ethnic group* (P < *0.0001*). C: *Incident diabetes by BMI category* (P *for trend* <*0.0001*). D: *Incident diabetes by quartiles of fasting insulin* (P *for trend* <*0.0001*).

bitrariness of IFG (16), we selected a fasting plasma glucose cutoff with specificity similar to IGT (Table 2). Fasting plasma glucose ≥5.4 mmol/l improved the predictive discrimination of the metabolic syndrome. Additionally, fasting glucose ≥5.4 mmol/l and/or at least three of the other NCEP requirements had a predictive discrimination similar to IGT and/or at least three of the other NCEP requirements.

Diabetes risk is associated with IGT and the metabolic syndrome (Fig. 2*A*) but is increased by obesity (Fig. 2*B* and *C*). Both IGT and the metabolic syndrome were independently associated with future risk of diabetes (Fig. 2*D*). Subjects meeting the NCEP definition requirements had a risk for diabetes sixfold higher than those without the NCEP definition requirements (Table 3). That risk was still threefold increased even after the adjustment for age, sex, ethnicity, family history of diabetes, IGT, and fasting insulin.

ROC curves illustrate the overall predictive discrimination of the 2-h glucose value, the NCEP criteria, and a modified version of the 1999 WHO criteria (Fig. 3). The area under the ROC curve for the NCEP criteria (0.776) was similar to the area of the 2-h glucose value (0.798, $P = 0.263$). The area for the modified WHO criteria (0.762) was similar to the areas of the 2-h glucose value ($P = 0.119$) and the NCEP criteria ($P = 0.314$). However, the area for the 2-h glucose value plus the NCEP (0.839) was greater than any of the other three areas ($P < 0.0001$).

**CONCLUSIONS** — We have demonstrated that IGT and the NCEP definition of the metabolic syndrome have comparable sensitivity for predicting diabetes. However, IGT had a higher positive predictive value than each of the definitions of the metabolic syndrome. In a population of mostly Mexican Americans, the NCEP definition detected more subjects at future risk for diabetes than a modified WHO definition that excluded the 2-h glucose requirement. In addition, changing the fasting plasma glucose requirement to ≥5.4 mmol/l improved the predictive discrimination of the metabolic syndrome.

Screening of asymptomatic adults is controversial because of the lack of evidence regarding the benefit of early diagnosis and treatment of diabetes (16,17). However, no study has been designed to answer this question. Support for early detection has the following bases: type 2 diabetes prevalence is rising to epidemic proportions (18), the high prevalence of undiagnosed diabetes (35% of diabetic subjects in the U.S.) (19), frequent diabetes-related complications at diagnosis (20), increased coronary artery disease mortality associated with IFG and IGT (21), and the prevention (or delay) of type 2 diabetes reported by lifestyle modification and medications (5–9).

IFG and IGT are both strong predictors of type 2 diabetes, although IGT is

**Table 2—*Sensitivity, specificity, and predicted values of IGT and the metabolic syndrome for identifying subjects at risk for type 2 diabetes***

| | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| IGT (2-h glucose ≥7.8 mmol/l in nondiabetic subjects) | 51.9 | 91.5 | 43.0 | 93.9 |
| IFG (fasting glucose ≥6.1 mmol/l in nondiabetic subjects) | 9.2 | 98.9 | 51.4 | 89.6 |
| NCEP definition | 52.8 | 84.9 | 30.8 | 93.4 |
| Modified WHO definition | 42.8 | 87.2 | 30.4 | 92.1 |
| NCEP definition and/or IGT | 70.8 | 79.1 | 29.7 | 95.6 |
| Modified WHO definition and/or IGT | 66.3 | 80.9 | 30.7 | 94.9 |
| Fasting plasma glucose requirement changed to ≥5.4 mmol/l | | | | |
| Fasting glucose ≥5.4 mmol/l | 42.6 | 91.7 | 39.3 | 92.6 |
| NCEP definition with fasting glucose ≥5.4 mmol/l* | 62.0 | 82.4 | 30.9 | 94.5 |
| Modified WHO definition with fasting glucose ≥5.4 mmol/l† | 49.5 | 85.4 | 30.6 | 92.9 |
| NCEP definition and/or a fasting glucose ≥5.4 mmol/l | 69.7 | 79.0 | 29.7 | 95.3 |
| Modified WHO definition and/or a fasting glucose ≥5.4 mmol/l | 60.3 | 81.1 | 29.3 | 94.0 |

*The NCEP definition with fasting glucose ≥5.4 mmol/l required at least three of the following: increased waist circumference (>102 cm in men and >88 cm in women), high triglycerides (≥1.7 mmol/l), low HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women), high blood pressure (≥130/85 mmHg or treated for hypertension), and fasting plasma glucose (≥5.4 mmol/l); †modified WHO definition with fasting glucose ≥5.4 mmol/l required fasting plasma glucose ≥5.4 mmol/l or hyperinsulinemia (fasting insulin in the top quartile of the nondiabetic population) plus at least two of the following: obesity (BMI ≥30 kg/m$^2$ or waist-to-hip ratio >0.9 in men and >0.85 in women), dyslipidemia (HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women or triglycerides ≥1.7 mmol/l), and hypertension (≥140/90 mmHg or treated for hypertension).

commonly only diagnosed in clinical research settings (16,22). IGT identifies more high-risk subjects than IFG. Conventional cardiovascular risk factors also have been shown to predict type 2 diabetes, especially if multivariable models are created by multiple logistic function analysis (23,24). However, those multivariable models are in need of validation in other epidemiological cohorts. The metabolic syndrome describes the clustering of risk factors associated with atherosclerosis and coronary heart disease. The NCEP definition has a clinical strategy with the objective of reducing the population burden of atherosclerosis (3), whereas the WHO definition has a more pathophysiological approach. The metabolic syndrome may be a good predictor of diabetes because insulin resistance, which is commonly associated with this clustering of metabolic factors, frequently precedes the onset of type 2 diabetes. Laaksonen et al. (14) have recently demonstrated that increased risk for diabetes is associated with the metabolic syndrome, and we have confirmed those results in our population.

Laaksonen et al. (14) have also described a better predictor of diabetes with the modified WHO definition than with the NCEP definition. Using those same definitions, we have observed a better predictive discrimination with the NCEP definition in a mostly Mexican-American population. This apparent discrepancy may be related to the following differences: targeted population (men in the Finnish study and men and women in the SAHS), definition of diabetes (1997 American Diabetes Association definition in the Finnish study and 1999 WHO definition in ours), diabetes risk (lower in the Finnish study than in the SAHS), phenotypic variation of the metabolic syndrome (more high blood pressure in Finnish subjects, and more obesity and dyslipidemia in the SAHS than in the Finnish study) (14,25), and the definition of insulin resistance by the upper quartile of fasting insulin in the nondiabetic population may not be equivalent between the Finnish study and the SAHS (14).

The modified WHO definition performs better in non-Hispanic whites than in Mexican Americans when both populations are considered separately. Since Mexican Americans have a higher diabetes prevalence and higher fasting insulin levels (12), the upper quartile of fasting insulin may identify a higher proportion of high-risk subjects in the non-Hispanic white population than in the Mexican-American population. These results agree with the better performance of the modified WHO definition in the Finnish study and suggest the need for a better definition of insulin resistance for epidemiological studies.

The metabolic syndrome is not better than IGT for detecting subjects at high risk for diabetes. However, the combination of IGT and the NCEP definition detects 70% of subjects at high risk for diabetes. Thus, adding the metabolic syndrome measurements to subjects undergoing an OGTT would be of prognostic if not therapeutic value.

Laaksonen et al. (14) have shown that excluding IFG from the definition of metabolic syndrome does not affect specificity. We have observed the same in our study. The overall contribution of IFG to the prevalence of the metabolic syndrome is low because of the low prevalence of IFG (2.2%). Davis (26) has suggested that IFG alone underestimates the burden of glucose disorders. In middle-aged Caucasian men, Von Eckardstein et al. (24) have demonstrated an improved ability to predict the risk for incident type 2 diabetes using a lower cut point for fasting plasma glucose (5.72 instead of 6.1 mmol/l). Since the cut point for fasting plasma glucose is somewhat arbitrary (16), we selected one that provides the impaired fasting glycemia requirement a specificity similar to IGT. The prediction of diabetes by the metabolic syndrome improves when using that fasting plasma glucose cutoff (≥5.4 mmol/l).

Without the consideration of other disorders, fasting plasma glucose ≥5.4 mmol/l performs well as a predictor of diabetes in the SAHS. Fasting plasma glucose ≥5.4 mmol/l in addition to at least three other NCEP definition requirements performs as well as the combination of IGT and/or at least three other NCEP definition requirements. Other

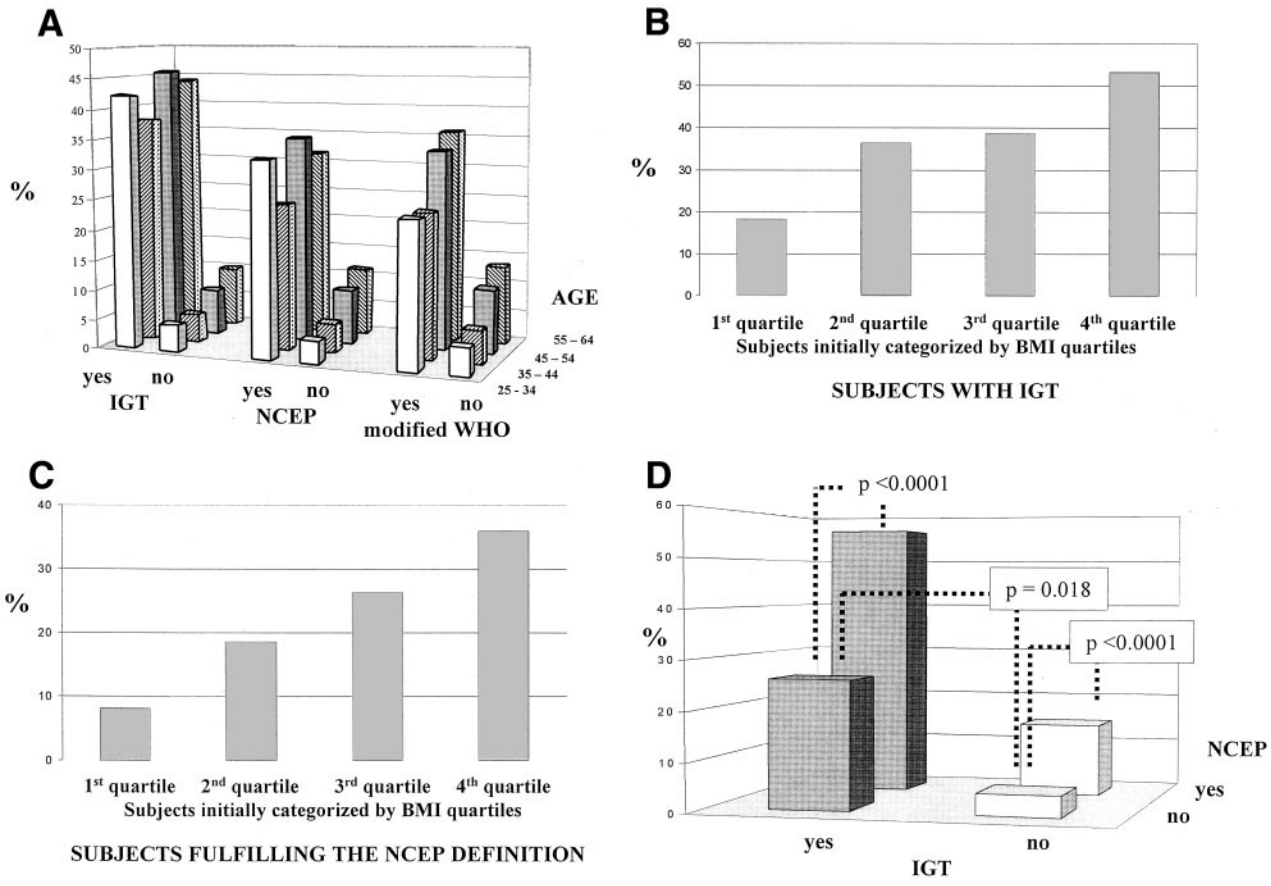


**Figure 2—***Diabetes risk associated with IGT or the metabolic syndrome after stratification by baseline age or BMI. A: Diabetes risk by age categories in subjects with IGT (*P *for trend = 0.676), the NECP definition (*P *for trend = 0.650), or the modified WHO definition (*P *for trend = 0.076). B: Age- and sex-adjusted incident diabetes in subjects initially categorized by quartiles of BMI who had IGT (*P *for the trend = 0.002). C: Age- and sex-adjusted incident diabetes in participants initially categorized by quartiles of BMI that fulfill the NCEP definition (*P *for trend = 0.006). D: Age- and sex-adjusted incident diabetes by IGT and the NCEP definition.*

studies need to validate our observation or to determine the optimal cut point of fasting plasma glucose for the prediction of diabetes.

Obesity worsens the diabetes risk associated with the metabolic syndrome or IGT. This is an expected finding because obesity is related to insulin resistance and a central element of the metabolic syndrome. Weight gain has been associated with higher incidence of the metabolic syndrome (27), and weight loss is associated with the prevention of type 2 diabetes (5–7) and lower mortality (28).

In summary, the metabolic syndrome increases the risk for diabetes independently of other risk factors, including IGT and fasting insulin. In a population of mostly Mexican Americans, the NCEP definition detects more subjects at future risk for diabetes than a modified WHO definition. Lowering the cutoff for fasting plasma glucose concentration to ≥5.4

**Table 3—***Multiple logistic regression analysis of incident diabetes with age, sex, family history of diabetes, NCEP definition, IGT, and fasting insulin as independent covariates*

| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|
| NCEP definition (yes vs. no) | 6.30 | 4.60–8.63 | 5.54 | 4.01–7.66 | 3.77 | 2.63–5.39 | 3.30 | 2.27–4.80 |
| Age (× 10-year interval) | — | — | 1.39 | 1.20–1.62 | 1.25 | 1.06–1.48 | 1.28 | 1.08–1.51 |
| Sex (men vs. women) | — | — | 0.87 | 0.62–1.20 | 0.99 | 0.69–1.42 | 0.93 | 0.64–1.33 |
| Mexican American vs. non-Hispanic white | — | — | 1.98 | 1.33–2.94 | 1.66 | 1.08–2.55 | 1.65 | 1.07–2.57 |
| Family history of diabetes (yes vs. no) | — | — | 1.68 | 1.21–2.34 | 1.74 | 1.21–2.49 | 1.77 | 1.23–2.54 |
| IGT (yes vs. no) | — | — | — | — | 7.00 | 4.84–10.1 | 6.37 | 4.37–9.28 |
| Fasting insulin (× 10-μU/ml interval) | — | — | — | — | — | — | 1.37 | 1.19–1.58 |

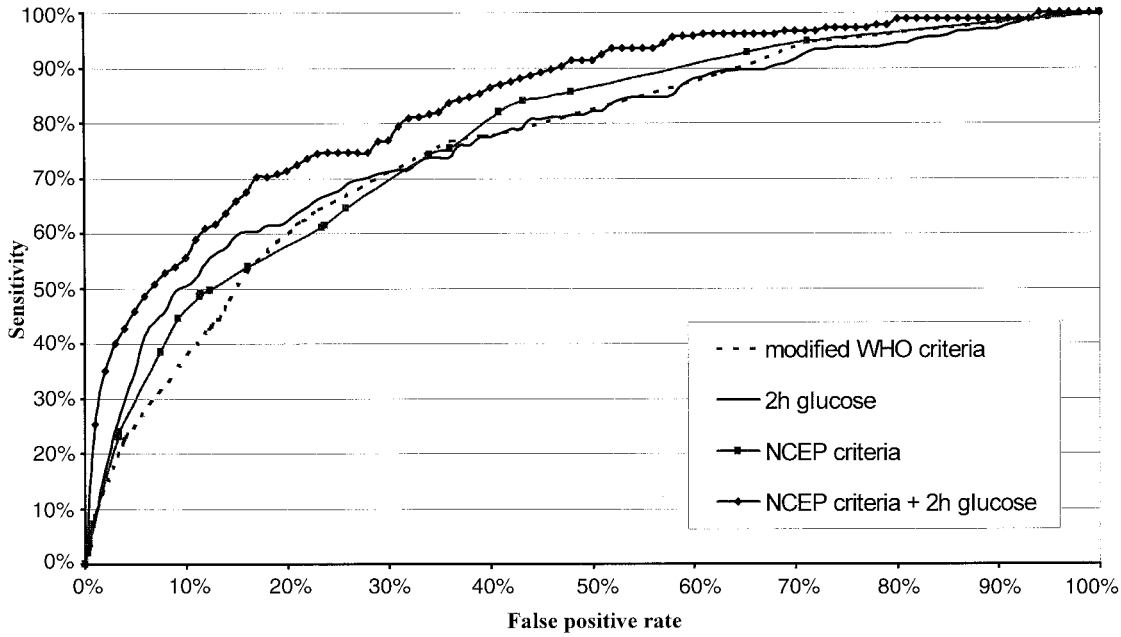


**Figure 3—***ROC curves for the prediction of type 2 diabetes.*

mmol/l improves the predictive discrimination of the metabolic syndrome.

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