

Using Metabolic Syndrome Traits for Efficient Detection of Impaired Glucose Tolerance

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CONCLUSIONS — The MetS, especially defined by IFG, large waist, and high triglycerides, efficiently identifies subjects likely to have IGT on OGTT and thus be eligible for diabetes prevention interventions.

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OBJECTIVE — Efficient detection of impaired glucose tolerance (IGT) is needed to implement type 2 diabetes prevention interventions.

RESEARCH DESIGN AND METHODS — We assessed the capacity of the metabolic syndrome (MetS) to identify IGT in a cross-sectional analysis of 3,326 Caucasian Framingham Offspring Study (FOS), 1,168 Caucasian and 1,812 Mexican-American San Antonio Heart Study (SAHS), 1,983 Mexico City Diabetes Study (MCDS), and 452 Caucasian, 407 Mexican-American, and 290 African-American Insulin Resistance Atherosclerosis Study (IRAS) men and women aged 30–79 years who had a clinical examination and an oral glucose tolerance test (OGTT) during 1987–1996. Those with diabetes treatment or fasting plasma glucose ≥ 7.0 mmol/l were excluded (MetS was defined by Third Report of the National Cholesterol Education Program's Adult Treatment Panel criteria and IGT as 2-h postchallenge glucose [2hPG] ≥ 7.8 mmol/l). We calculated positive (PPV) and negative predictive values (NPV), population attributable risk percentages (PAR%), age- and sex-adjusted odds ratios (ORs), and areas under the receiver operating characteristic curve (AROCs) associated with MetS traits.

RESULTS — Among FOS, SAHS, and MCDS subjects, 24–43% had MetS and 15–23% had IGT (including 2–5% with 2hPG ≥ 11.1 mmol/l). Among those with MetS, OR for IGT were 3–4, PPV were 0.24–0.41, NPV were 0.84–0.91, and PAR% were 30–40%. Among subjects with MetS defined by impaired fasting glucose (IFG) and any two other traits, OR for IGT were 9–24, PPV were 0.62–0.89, NPV were 0.78–0.87, and PAR% were 3–12%. Among IRAS subjects, 24–34% had MetS and 37–41% had IGT. Among those with MetS, ORs for IGT were 3–6, PPVs were 0.57–0.73, and NPVs were 0.67–0.72. In logistic regression models, IFG, large waist, and high triglycerides were independently associated with IGT (AROC 0.71–0.83) in all study populations.

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Abbreviations: AR%, attributable risk percentage; AROC, area under the receiver operating characteristic curve; FOS, Framingham Offspring Study; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; MCDS, Mexico City Diabetes Study; MetS, metabolic syndrome; NCEP ATP III, Third Report of the National Cholesterol Education Program's Adult Treatment Panel III; NPV, negative predictive value; PAR%, population attributable risk; PPV, positive predictive value; OGTT, oral glucose tolerance test; SAHS, San Antonio Heart Study; 2hPG, 2-h postchallenge glucose.

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

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The prevalence of type 2 diabetes is rapidly growing worldwide, with rates expected to increase $>165\%$ by 2050 in the U.S. alone (1). Diabetes and its complications cause substantial loss in length and quality of life and incur $> \$132$ billion annually in U.S. health care expenditures (2). There are few conditions with a more pernicious effect than diabetes on patient health and health care budgets.

Fortunately, there is good experimental evidence that type 2 diabetes can be prevented or delayed. Lifestyle modification with diet and exercise, or use of metformin or acarbose, can reduce risk of type 2 diabetes in individuals with impaired glucose tolerance (IGT) by 30–70% with ~ 7 –14 affected people needing treatment for ~ 3 years to prevent one case of diabetes (3–6). Given that ~ 12 million U.S. adults may be eligible for these proven diabetes prevention interventions (7) and that they are effective, relatively safe, and feasible clinical and public health strategies, their broad implementation is now an urgent priority.

An important impediment to wider translation of evidence-based diabetes prevention is the apparent need to identify people with IGT. IGT is defined using an oral glucose tolerance test (OGTT) as a plasma glucose level of 7.8–11.0 mmol/l level 2 h after oral glucose challenge (2hPG) in individuals with nondiabetic fasting plasma glucose levels (< 7.0 mmol/l) (8). Although fasting plasma glucose (FPG) in the “impaired” (IFG) range (6.1–6.9 mmol/l) is also a risk factor for type 2 diabetes, in many studies, IGT has been a stronger risk factor for diabetes than IFG (9–12). Approximately 30–

60% of subjects with IGT have normal fasting glucose levels, so fasting testing alone does not detect many subjects at risk for diabetes on the basis of hyperglycemia (11,13,14). Because IGT was the glycemic entry criteria for recent diabetes prevention trials, an OGTT appears to be required for evidence-based identification of eligible subjects. In the U.S., the OGTT is considered to entail enough discomfort, inconvenience, and expense that the test is not encouraged for use in usual clinical practice (15). Efficient means to identify subjects most likely to have IGT on OGTT are needed to maximize implementation of evidence-based type 2 diabetes prevention interventions.

IGT and type 2 diabetes are closely associated with cardiovascular disease and may originate from a common physiological antecedent, the "insulin resistance" or "metabolic" syndrome (16,17). Traits of the metabolic syndrome (MetS) (IFG, obesity, dyslipidemia, and hypertension) are readily identifiable in clinical practice and may help to identify subjects eligible for an OGTT. These traits have recently been shown to be excellent predictors of incident type 2 diabetes (18), but their use to identify prevalent IGT has not been explored. In this report, we analyzed data from four large epidemiological studies (the Framingham Offspring, San Antonio Heart, Mexico City Diabetes, and Insulin Resistance Atherosclerosis Studies) to identify a population subset with a high probability of IGT based on IFG and nonglycemic traits of the MetS.

RESEARCH DESIGN AND METHODS

Source datasets

The Framingham Offspring Study (FOS) and the other datasets have been described previously and will be presented only briefly here. The FOS is a population-based observational study of risk factors for cardiovascular diseases. Participants are the children and spouses of the children of the original Framingham Heart Study cohort and are of mixed European Caucasian race/ethnicity (19,20). The Institutional Review Board of Boston University approved the study protocol, and all subjects gave informed consent at each examination. Data were taken from the fifth examination cycle (January 1991–June 1995) when 3,799 participants fasted overnight, had a standard-

ized medical history, physical, and laboratory examination, and those without diagnosed diabetes had an OGTT. Subjects had diagnosed diabetes if they reported hypoglycemic drug therapy or if the FPG was ≥ 7.0 mmol/l at any two prior examinations. Height, weight, and waist circumference (at the umbilicus with the subject standing) were measured, and BMI was calculated as kg/m^2 . Two blood pressure measurements were taken after subjects had been seated for at least 5 min; the averaged blood pressure value was used. Plasma glucose was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was $< 3\%$. Levels of fasting plasma triglycerides and HDL cholesterol were measured as previously described (21,22).

The San Antonio Heart Study (SAHS) is a population-based observational study of diabetes and cardiovascular disease (23–25). The study initially enrolled 3,301 Mexican-American and 1,857 non-Hispanic Caucasian men and nonpregnant women in two phases between 1979 and 1988. Participants were 25–64 years of age at enrollment and were randomly selected from low-, middle-, and high-income neighborhoods in San Antonio, Texas. An 8-year follow-up examination was conducted from 1987 to 1996. A total of 3,682 individuals (73.7% of survivors) from the two phases completed the follow-up examination. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the study protocol, and all subjects gave informed consent at each examination. Data for the present analysis came from the follow-up examination so as to be contemporaneous with other datasets. Three blood pressure measurements were taken after subjects had been seated for at least 5 min; the average of the second two blood pressure values were used, and glucose levels were measured with the glucose oxidase method. Apart from these two differences, the rest of the clinical examination, the definition of diagnosed diabetes, and the laboratory analysis methods were similar to those used in the FOS.

The Mexico City Diabetes Study (MCDS) is a population-based study of type 2 diabetes in six low-income "colonias" in Mexico City (26). A complete

enumeration of the colonias was carried out, and 3,326 study-eligible men and nonpregnant women age 35–64 years were identified. Of these, 2,813 completed a home interview, and 2,282 (68.5%) completed a baseline medical examination during 1990–1992. The Institutional Review Boards of the Centro de Estudios en Diabetes in Mexico City and the University of Texas Health Science Center at San Antonio approved the study protocol, and all subjects gave informed consent. Data for the present analysis was taken from the baseline examination. The clinical examination and definitions of diagnosed diabetes were identical to those used in the SAHS. Laboratory analyses were conducted in San Antonio in the Division of Clinical Epidemiology laboratory using methods similar to those used in the SAHS (27).

The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, observational study of the relationship between insulin resistance and cardiovascular disease risk factors (28,29). Unlike the unselected FOS, SAHS, and MCDS samples, the IRAS sample was selected to give roughly equal numbers of subjects with normal, impaired, and diabetic glucose tolerance in roughly equally sized groups of Caucasian, Mexican-American, and African-American subjects. The study was conducted at four clinical centers. At centers in Oakland and Los Angeles, California, non-Hispanic Caucasian and African-American individuals were recruited from Kaiser Permanente, a non-profit health maintenance organization. Centers in San Antonio, Texas, and San Luis Valley, Colorado, recruited Caucasian and Mexican-American individuals from two ongoing population-based studies (the SAHS and the San Luis Valley Diabetes Study). A total of 1,625 subjects participated in the baseline IRAS examination during 1992–1994, during which an OGTT was administered. Local institutional review committees approved the IRAS protocol, all participants provided written informed consent, and the clinical and laboratory examinations were conducted using methods similar to those used in the SAHS and MCDS.

Definitions of outcome and exposure variables

The overall goal of this analysis was to identify prevalent IGT in a population setting using a typical clinical examination

and a fasting blood test. With this approach, people with FPG levels diagnostic of diabetes would be detected and removed from consideration for an OGTT. However, the sample would still contain a small percentage with nondiabetic FPG levels but diabetic range postchallenge glucose levels who would not be detected without an OGTT, but who would still be included in the cohort identified for preventive interventions. Therefore, for the purposes of this analysis, we defined IGT as all subjects with FPG <7.0 mmol/l and with 2hPG \geq 7.8 mmol/l, including those few with 2hPG \geq 11.1 mmol/l.

We used criteria proposed by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) to classify the MetS and its traits (30). We considered the following traits alone, in pairs, or in combinations of three: FPG \geq 6.1 mmol/l; waist circumference >102 cm (in men) or >88 cm (in women); fasting triglycerides \geq 1.7 mmol/l; HDL cholesterol <1.0 mmol/l (in men) or <1.16 mmol/l (in women); and blood pressure \geq 130/85 mmHg (or treatment for hypertension). Subjects with any three traits were considered to have the MetS by ATP III criteria. Additional exposure covariates included age, sex, and race/ethnicity. In subsidiary analyses we also considered the effect of the recently proposed lower threshold for IFG of FPG 5.6–6.9 mmol/l (31).

Statistical analysis

Analyses were conducted using SAS (SAS Institute, Cary, NC). Subjects with diagnosed diabetes, FPG \geq 7.0 mmol/l, age <30 or >79 years, or missing covariates were excluded. All analyses were stratified by study and race/ethnicity. We described the prevalence of MetS traits and of IGT, then assessed the probability of IGT (positive predictive value [PPV]) or absence of IGT (negative predictive value [NPV]) associated with traits alone, in pairs, or in combinations of three (the MetS) in which PPV = (the number of subjects with the trait and IGT/the number of subjects with the trait) and NPV = (the number of subjects without the trait and without IGT/the number of subjects without the trait). We used age- and sex-adjusted logistic regression models to calculate the odds ratio (OR) for IGT associated with MetS and MetS traits and to calculate areas under the receiver operating characteristic curve (AROCs). The

AROC is interpreted as the probability that the modeled trait(s) would correctly discriminate subjects with IGT from those without IGT in which 0.5 is chance discrimination and 1.0 is perfect discrimination.

We also estimated the attributable risk percentage (AR%) for IGT associated with MetS and MetS traits. AR% can be thought of as the excess risk of IGT attributable to MetS or a given trait. We calculated AR% as [relative risk – 1.0]/relative risk \times 100. For the unselected samples (FOS, SAHS, MCDS) where the true trait prevalence p_{trait} was known, we also estimated the population attributable risk percent (PAR%), interpreted as the proportion of IGT in the total population associated with MetS or its traits, and the proportion that might be eliminated given treatment of the trait(s) to normal levels in which PAR% = $(p_{\text{trait}} \times [\text{relative risk} - 1]) / (p_{\text{trait}} \times [\text{relative risk} - 1] + 1) \times 100$.

Finally, we estimated the independent risk of IGT associated with MetS traits by simultaneously including all five traits in age- and sex-adjusted multivariate logistic regression models. We constructed study- and race/ethnicity-stratified regression models using each study's own data, then compared the equality of ORs and model discrimination and calibration using FOS model results as the reference, as previously described (32). We compared ORs by comparing risk factor regression coefficients for the FOS and non-FOS cohorts. To compare these coefficients we calculated a test statistic z , in which $z = [b(F) - b(O)]/SE$, and where $b(F)$ and $b(O)$ are, respectively, the regression coefficients of the FOS and the other study's model, whereas SE is the standard error of the difference in the coefficients. This is computed as the square root of the sum of the squares of the SEs for the two coefficients. Because the OR of a variable is computed by exponentiating its regression coefficient, the z statistic tests the equality of ORs between FOS and non-FOS cohorts. Using this procedure, we made six statistical comparisons for each risk factor and so defined statistical significance as a two-tailed P value \leq 0.008. Discrimination was assessed by calculation of the AROC, first for each study using its own data and then by applying the regression equation generated from FOS data to each set of study data. Calibration, or how closely predicted outcomes agree with actual outcomes, was assessed with a version of the Hosmer-

Lemeshow χ^2 statistic comparing the differences between predicted and actual event rates with values exceeding 20 indicating significant lack of calibration ($P < 0.01$) and small values indicating good calibration. We assessed calibration first for each study using its own data, then by applying the regression equation generated from FOS data to each set of study data. We then recalibrated FOS model-based results for each study by adjusting the intercept for the study's own event rate and risk factor mean values, as previously described (32). It is important to emphasize that recalibration does not affect OR comparisons or discrimination results.

RESULTS— Subject characteristics stratified by study and race/ethnicity are displayed in Table 1. A little more than one-half of subjects were women, and the mean age ranged from 46 to 59 years. Of the 9,438 study subjects, 52.4% were Caucasian, 44.5% were Mexican or Mexican American, and 3.1% were African American. In general, Mexican and Mexican-American subjects in the population-based studies had a higher prevalence of adverse metabolic traits than did Caucasian subjects, as observed previously (33). From 69 to 88% of subjects had a BMI \geq 24 kg/m² (an entry criteria for the Diabetes Prevention Program) (5), and 23–36% had a BMI \geq 30 kg/m², which was the National Institutes of Health–recommended threshold defining medical obesity (34). From 24 to 43% of the unselected samples and 25 to 34% of the IRAS samples had the ATP III–defined MetS. By design, IRAS participants had a higher prevalence of IGT (37–41%) than did participants in the unselected samples (15–23%). Clinically undetected, diabetic-range postchallenge hyperglycemia was modestly common, affecting 1.7–5.4% of the unselected samples and 6.8–11.2% of the IRAS sample.

The prevalence of MetS traits and their associations with IGT among FOS, SAHS, and MCDS subjects are displayed in Table 2 and among IRAS subjects in Table 3. For simplicity of presentation, trait combinations are sorted in descending order of ORs for IGT among FOS Caucasians. The distribution of MetS and its traits varied widely within and across populations. IFG was the least common trait in all study populations, affecting 3–8% of the population-based samples

Table 1—Characteristics of the FOS, SAHS, MCDS, and IRAS subjects

	FOS Caucasian	SAHS		MCDS Mexican	IRAS		
		Non-Hispanic Caucasian	Mexican American		Non-Hispanic Caucasian	Mexican American	African American
n	3,326	1,168	1,812	1,983	452	407	290
Women	54.0	56.0	59.0	59.0	53.4	59.0	58.5
Age (years)	54 ± 9.8	52.8 ± 11.3	46.5 ± 8.1	46.5 ± 8.1	56.2 ± 8.4	46.5 ± 8.1	54.9 ± 8.6
BMI ≥24 kg/m ²	73.2	69.3	83.9	84.6	77.6	85.3	87.8
BMI ≥30 kg/m ²	23.2	22.6	35.8	28.1	27.0	30.6	34.8
MetS-NCEP ATP III	25.9	23.5	28.7	43.3	25.4	34.2	24.4
2hPG ≥7.8 mmol/l	14.5	15.9	23.3	15.8	36.8	41.3	39.1
2hPG ≥11.1 mmol/l	1.7	2.4	5.4	2.6	6.8	11.2	8.4

Data are means ± SD or %.

and 16–26% of the IRAS sample. All other traits affected at least 26% of subjects with low HDL cholesterol, which was the most common trait (up to 92% of Mexicans in the MCDS), except in African-American IRAS participants, where high triglyceride levels were relatively infrequent (15%) and hypertension was most common (61%). Consequently, combinations of two or three traits, including IFG, were also substantially less prevalent than trait combinations without IFG. However, IFG alone or in combination with other traits conferred substantially higher risk of IGT (for instance, ORs 8–43 in the unselected samples) compared with any trait combination without IFG (ORs 1.2–4) and had reasonable discriminatory capacity (AROC 0.616–0.805). In all study populations, subjects with IFG alone or in combination were very likely also to have IGT (PPV 0.54–0.95), whereas subjects without IFG were unlikely to have IGT (NPV 0.61–0.89). IFG alone or with other traits accounted for a large proportion of risk of IGT among subjects in the unselected samples (AR% 69–83%), but the low prevalence of IFG translated to relatively low PAR% (3–23%). So, for instance, IFG and high triglycerides affected 4% of FOS Caucasian subjects but increased the odds of IGT by 14-fold; 67% of these subjects had IGT, but 88% of those without IFG and high triglycerides did not have IGT. IFG and high triglycerides accounted for 82% of the risk of IGT in affected subjects and 16% of IGT on a population-wide basis.

The MetS is defined by ATP III as the presence of any three of the five traits under consideration. In all populations, MetS by this definition was more prevalent but associated with lower risk, better discriminatory capacity, lower PPV,

higher NPV, lower AR%, and higher PAR% than the MetS defined by IFG plus two other traits (Tables 2 and 3). Interestingly, if the MetS were redefined as any two traits, it became more prevalent, but its ability to detect IGT was not substantially poorer than that of the MetS defined by any three traits. So, for instance, any two traits affected 58% and any three traits affected 29% of SAHS Mexican-American subjects, but these were associated with ORs of 3.1 and 3.2 and PPVs of 0.88 and 0.84, respectively.

In multivariable logistic regression models, IFG remained the strongest independent predictor of IGT in all study populations, increasing odds of IGT by 3- to over 12-fold (Table 4). High triglycerides and a large waist circumference were also consistent, strong, independent risk factors for IGT, increasing odds by 1.5- to ~4-fold. In SAHS and IRAS Caucasian subjects, a large waist was a significantly stronger risk factor than in FOS Caucasian subjects, but all other risk factors conferred statistically similar risk in all populations, suggesting that these MetS traits perform similarly in Caucasian, Mexican, and African-American populations to identify IGT. Low levels of HDL cholesterol were not independently associated with risk of IGT in any population, and elevated blood pressure was a risk factor only in FOS Caucasian, SAHS Mexican-American, and MCDS Mexican subjects. These models provided reasonable discrimination of IGT (AROC 0.71–0.83) and statistically acceptable calibration (all χ^2 statistics <20). Calibration of the FOS-derived model, when applied to the other cohorts' data, was substantially improved with recalibration. Notably, the degree of discrimination from multivariate prediction models in all datasets was not sub-

stantially better than that obtained with simple combinations of two or three traits.

The American Diabetes Association recently recommended that the lower threshold for IFG be reduced from 6.1 to 5.6 mmol/l (31), so we examined the effect on IGT prediction of the lower IFG criteria. In all populations, compared with the higher threshold of FPG ≥6.1 mmol/l, the prevalence of IFG ≥5.6 mmol/l was higher, and for "IFG"-based MetS definitions, the PAR% values were higher, ORs and PPVs for IGT were reduced, AROCs were similar or slightly higher, and NPVs were higher (Table 5). In the unselected populations, the ATP III MetS using "IFG" as one of three possible traits was slightly more common and associated with a slightly higher PAR% but with similar or only marginally higher ORs, PPVs, AROCs, and NPVs; in IRAS subjects, these increases were somewhat larger. In the sets of multivariate regression models predicting IGT, ORs for IFG ≥5.6 mmol/l were lower than in the sets of models using IFG ≥6.1 mmol/l, but AROCs for the two sets of models were essentially identical (Table 5); ORs for the other MetS traits and the calibration statistics also were very similar when comparing the two sets of models (data not shown).

The focus of this analysis was to define a strategy to identify people without clinical diabetes who would fail an OGTT. In our data, the majority of these had IGT as strictly defined by 2hPG 7.8–11.0 mmol/l, but a few had diabetes on the basis of 2hPG ≥11.1 mmol/l. The ATP III MetS had a similar capacity to identify 2hPG ≥11.1 mmol/l as for 2hPG ≥7.8 mmol/l. In the unselected samples, the ORs were 4.1–6.2, AROCs were 0.77–0.82, PPVs were 5–12%, NPVs were 97–99%,

Table 2—Association of IGT (2hPG \geq 7.8 mmol/l) with traits of the MeIs in the FOS, SAHS, and MCDS

	FOS Caucasian				SAHS Non-Hispanic Caucasian				SAHS Mexican American				MCDS Mexican				
	P(O)	OR	AROC	PPV NPV %	AR PAR %	P(O)	OR	AROC	PPV NPV %	AR PAR %	P(O)	OR	AROC	PPV NPV %	AR PAR %		
IFG (FPG 6.1–6.9 mmol/l)	0.08	8.21	0.751	0.54 0.89	79.5 23.6	0.03 10.9	0.688	0.63 0.86	77.6 10.7	0.06 8.89	0.717	0.68 0.80	70.2 13.0	0.03 14.2	0.654	0.71 0.86	80.4 11.8
High TG (\geq 1.7 mmol/l)	0.33	2.99	0.735	0.25 0.91	63.0 36.1	0.34 2.32	0.678	0.24 0.88	51.6 26.3	0.42 2.02	0.690	0.30 0.82	40.2 22.1	0.60 2.54	0.658	0.20 0.91	53.8 41.1
High BP (\geq 130/85 mmHg or Rx)	0.46	2.50	0.717	0.22 0.92	64.7 45.6	0.28 1.75	0.649	0.24 0.87	45.9 19.3	0.28 2.41	0.695	0.38 0.82	52.4 23.5	0.26 1.90	0.634	0.24 0.87	47.2 18.7
Large waist circumference (>102/88 cm, men/women)	0.34	2.17	0.710	0.22 0.89	51.9 26.8	0.39 3.43	0.715	0.27 0.91	65.9 42.8	0.46 2.50	0.706	0.33 0.85	55.9 37.0	0.53 2.00	0.629	0.20 0.89	44.6 30.0
Low HDL-C (<1.0/1.16 mmol/l, men/women)	0.38	1.96	0.707	0.20 0.89	42.7 22.0	0.55 1.58	0.651	0.18 0.87	25.8 16.0	0.59 1.54	0.675	0.26 0.81	25.5 16.8	0.92 1.18	0.602	0.16 0.86	12.9 12.0
IFG and high TG	0.04	14.0	0.739	0.67 0.88	81.7 15.9	0.02 17.2	0.668	0.71 0.85	79.2 6.3	0.04 13.6	0.703	0.78 0.79	72.9 9.6	0.02 24.1	0.651	0.80 0.86	82.3 9.7
IFG and large waist	0.05	9.65	0.731	0.61 0.88	80.1 16.1	0.02 14.5	0.665	0.70 0.85	78.7 6.7	0.04 8.27	0.699	0.70 0.79	69.4 8.6	0.02 11.3	0.630	0.69 0.86	79.0 8.3
IFG and high BP	0.04	9.45	0.733	0.59 0.87	78.9 13.6	0.02 13.8	0.657	0.71 0.85	79.2 6.3	0.03 12.4	0.694	0.78 0.78	72.3 7.3	0.01 17.5	0.626	0.78 0.85	80.8 5.4
IFG and low HDL-C	0.06	8.19	0.732	0.57 0.88	79.2 18.4	0.02 14.5	0.681	0.68 0.85	78.5 7.9	0.04 11.3	0.707	0.74 0.79	71.7 9.8	0.03 14.0	0.649	0.71 0.86	80.1 10.5
High TG and high BP	0.20	3.24	0.736	0.31 0.90	66.1 28.2	0.13 2.21	0.645	0.29 0.86	51.4 12.0	0.15 2.77	0.693	0.42 0.80	52.9 14.7	0.18 2.52	0.647	0.29 0.87	55.6 18.1
High TG and low waist	0.16	2.89	0.720	0.29 0.88	60.2 19.4	0.19 3.70	0.677	0.24 0.88	65.4 26.4	0.23 2.32	0.696	0.38 0.81	49.1 17.8	0.33 2.30	0.654	0.24 0.88	52.7 26.8
High TG and low HDL-C	0.21	2.82	0.727	0.27 0.89	58.5 22.9	0.24 2.36	0.670	0.25 0.87	47.7 18.3	0.31 1.87	0.686	0.31 0.80	37.0 15.2	0.57 2.31	0.653	0.20 0.90	50.2 36.6
Large waist and high BP	0.21	2.74	0.722	0.29 0.89	62.4 25.6	0.14 2.72	0.662	0.33 0.87	60.2 17.0	0.16 2.67	0.692	0.44 0.81	56.7 17.7	0.16 1.83	0.626	0.26 0.86	48.0 13.2
Large waist and low HDL-C	0.17	2.36	0.710	0.25 0.88	51.7 15.4	0.26 2.93	0.696	0.27 0.88	56.7 25.0	0.31 2.11	0.695	0.34 0.81	45.6 20.4	0.51 1.76	0.622	0.20 0.88	40.2 25.4
Low HDL-C and high BP	0.20	2.17	0.711	0.26 0.88	54.5 19.5	0.16 2.04	0.651	0.27 0.86	47.9 12.7	0.16 2.41	0.687	0.40 0.80	50.1 13.9	0.23 1.77	0.630	0.24 0.87	44.4 15.7
Any two traits	0.47	4.34	0.757	0.24 0.94	75.5 59.2	0.49 3.04	0.698	0.23 0.92	63.9 46.6	0.58 3.12	0.718	0.32 0.88	62.4 48.9	0.81 3.39	0.637	0.18 0.95	70.2 65.5
IFG, high TG, high BP	0.03	13.2	0.723	0.67 0.87	81.1 12.1	0.01 28.6	0.649	0.80 0.85	80.8 3.4	0.02 25.8	0.689	0.89 0.78	75.1 5.5	0.01 43.0	0.625	0.89 0.85	83.0 4.2
IFG, high TG, low HDL-C	0.03	13.1	0.727	0.66 0.87	80.4 11.2	0.02 14.9	0.664	0.68 0.85	78.0 5.4	0.03 14.3	0.696	0.80 0.78	73.0 7.5	0.02 22.6	0.648	0.80 0.86	82.0 9.2
IFG, high TG, large waist	0.03	12.5	0.718	0.67 0.87	80.7 10.4	0.01 20.4	0.657	0.75 0.85	79.9 5.1	0.03 12.7	0.688	0.79 0.78	7.2 6.3	0.02 18.8	0.631	0.79 0.85	81.4 6.8
IFG, large waist, low HDL-C	0.03	10.8	0.717	0.64 0.87	79.7 9.6	0.02 14.4	0.661	0.68 0.85	78.0 5.4	0.03 11.0	0.695	0.75 0.78	70.8 6.8	0.02 11.4	0.629	0.69 0.85	78.9 7.8
Large waist, high TG, low HDL-C	0.11	3.06	0.714	0.31 0.88	60.1 13.8	0.15 3.66	0.694	0.34 0.87	62.1 19.5	0.17 2.26	0.692	0.38 0.80	47.2 13.4	0.32 2.14	0.649	0.24 0.88	50.0 24.1
High TG, low HDL-C, high BP	0.13	2.78	0.719	0.31 0.88	60.6 17.0	0.09 2.31	0.645	0.29 0.85	49.2 8.1	0.11 2.60	0.685	0.43 0.79	50.6 9.9	0.17 2.38	0.644	0.29 0.87	53.8 16.3
Large waist, low HDL-C, high BP	0.11	2.65	0.710	0.30 0.87	58.8 13.5	0.08 2.93	0.654	0.35 0.86	59.6 10.8	0.10 2.62	0.683	0.45 0.79	54.1 10.9	0.16 1.73	0.623	0.26 0.86	45.7 11.5
Any three traits (MeIs)	0.26	3.92	0.757	0.31 0.91	71.1 38.9	0.24 4.03	0.718	0.33 0.89	67.8 33.5	0.29 3.24	0.726	0.41 0.84	60.3 30.6	0.43 2.80	0.669	0.24 0.91	61.1 40.4

BP, blood pressure; HDL-C, HDL cholesterol; P(O), prevalence of the trait or trait combination; TG, fasting triglycerides.

Table 3—Association of IGT (2hPG ≥7.8 mmol/l) with traits of the MetS in the IRAS

	IRAS																	
	Non-Hispanic Caucasian						Mexican American						African American					
	P(t)	OR	AROC	PPV	NPV	AR%	P(t)	OR	AROC	PPV	NPV	AR%	P(t)	OR	AROC	PPV	NPV	AR%
IFG (FPG 6.1–6.9 mmol/l)	0.16	3.65	0.671	0.62	0.68	48.2	0.17	6.92	0.721	0.77	0.66	56.5	0.26	13.1	0.805	0.81	0.76	69.7
High TG (≥1.7 mmol/l)	0.31	2.00	0.656	0.47	0.68	32.7	0.42	2.75	0.694	0.55	0.69	43.2	0.15	1.39	0.635	0.47	0.62	19.2
High BP (≥130/85 mmHg or Rx)	0.44	1.67	0.641	0.45	0.70	31.7	0.44	1.82	0.653	0.52	0.67	35.2	0.61	2.02	0.653	0.48	0.73	43.6
Large waist circumference (>102/88 cm, men/women)	0.29	4.83	0.719	0.64	0.74	59.8	0.32	2.89	0.687	0.59	0.67	44.3	0.36	3.63	0.707	0.57	0.71	48.9
Low HDL-C (<1.0/1.16 mmol/l, men/women)	0.49	1.58	0.643	0.41	0.68	21.3	0.63	1.61	0.648	0.45	0.65	22.1	0.35	1.49	0.642	0.43	0.63	15.4
IFG and high TG	0.04	7.17	0.658	0.79	0.65	55.8	0.09	8.21	0.688	0.82	0.63	54.4	0.05	23.5	0.671	0.93	0.64	60.7
IFG and large waist	0.07	20.8	0.683	0.91	0.67	64.2	0.10	11.5	0.688	0.88	0.64	58.8	0.14	11.0	0.735	0.83	0.68	61.7
IFG and high BP	0.09	3.37	0.648	0.64	0.66	46.6	0.11	4.91	0.680	0.75	0.63	50.3	0.19	8.33	0.749	0.79	0.70	61.8
IFG and low HDL-C	0.09	3.05	0.647	0.62	0.66	44.7	0.12	9.38	0.703	0.83	0.64	57.1	0.10	8.34	0.701	0.80	0.65	56.8
High TG and high BP	0.15	2.11	0.643	0.53	0.66	36.0	0.22	2.37	0.669	0.59	0.64	39.1	0.08	1.70	0.643	0.54	0.62	30.2
High TG and large waist	0.12	3.48	0.659	0.65	0.67	49.1	0.16	3.39	0.683	0.66	0.63	44.3	0.07	3.22	0.649	0.67	0.63	44.4
High TG and low HDL-C	0.21	1.67	0.640	0.46	0.66	26.4	0.33	2.49	0.682	0.56	0.66	38.9	0.10	1.89	0.641	0.52	0.62	27.0
Large waist and high BP	0.18	4.18	0.679	0.67	0.70	55.0	0.19	2.11	0.657	0.58	0.63	36.1	0.25	2.98	0.682	0.59	0.68	45.4
Large waist and low HDL-C	0.18	4.27	0.694	0.65	0.70	53.1	0.24	2.20	0.661	0.56	0.63	33.8	0.16	3.08	0.661	0.57	0.64	37.8
Low HDL-C and high BP	0.20	1.75	0.640	0.48	0.66	30.2	0.27	1.64	0.645	0.52	0.63	28.7	0.19	3.02	0.676	0.61	0.66	43.7
Any two traits	0.53	3.30	0.701	0.49	0.77	52.7	0.61	4.64	0.726	0.55	0.80	63.6	0.54	4.59	0.734	0.54	0.79	61.0
IFG, high TG, high BP	0.02	13.1	0.639	0.88	0.64	59.0	0.07	7.41	0.673	0.81	0.62	52.8	0.03	10.2	0.646	0.88	0.62	56.8
IFG, high TG, low HDL-C	0.03	5.65	0.643	0.77	0.64	53.7	0.08	17.4	0.690	0.90	0.63	58.7	0.03	16.3	0.660	0.90	0.63	58.5
IFG, high TG, large waist	0.02	*	*	*	*	*	0.06	10.3	0.667	0.87	0.61	55.6	0.03	10.4	0.647	0.88	0.62	56.8
IFG, large waist, low HDL-C	0.05	16.5	0.658	0.90	0.66	62.2	0.07	14.4	0.678	0.90	0.63	58.4	0.06	6.77	0.672	0.78	0.63	52.9
IFG, large waist, high BP	0.05	18.7	0.661	0.91	0.66	62.9	0.07	6.31	0.660	0.81	0.62	52.8	0.10	7.52	0.703	0.80	0.65	56.8
IFG, low HDL-C, high BP	0.04	2.16	0.626	0.58	0.64	38.1	0.07	7.46	0.670	0.82	0.62	53.3	0.07	7.99	0.681	0.81	0.64	55.6
Large waist, high TG, high BP	0.08	3.48	0.647	0.67	0.66	48.7	0.10	3.07	0.667	0.67	0.62	42.4	0.04	3.49	0.645	0.69	0.62	45.5
Large waist, high TG, low HDL-C	0.09	2.80	0.650	0.61	0.66	43.6	0.14	3.09	0.672	0.64	0.62	41.4	0.05	6.60	0.654	0.79	0.63	52.7
High TG, low HDL-C, high BP	0.10	1.86	0.636	0.52	0.65	32.8	0.17	2.24	0.661	0.60	0.63	37.6	0.06	2.96	0.647	0.65	0.62	41.9
Large waist, low HDL-C, high BP	0.10	3.80	0.658	0.67	0.67	50.5	0.13	1.72	0.642	0.55	0.61	28.0	0.09	4.57	0.668	0.70	0.64	48.8
Any three traits (MetS)	0.25	4.42	0.709	0.64	0.72	56.8	0.34	2.52	0.680	0.57	0.67	42.1	0.24	6.62	0.747	0.73	0.72	61.0

For abbreviations, see footnote to Table 2. IRAS subjects were selected for the presence of IGT. *All subjects with IFG, high TG, and large waist had IGT.

and PAR% were 55–77%. In the IRAS subjects, the ORs were 2.0–5.4, AROCs 0.70–0.75, PPVs were 14–21%, and NPVs were 92–96%.

CONCLUSIONS— Clinical interventions effectively prevent or delay type 2 diabetes among individuals with IGT (3–6). Now we need clinical strategies to identify people with IGT to maximize translation of this evidence into practice. Aversion to routine clinical use of the OGTT may need to be replaced by targeted clinical screening of people likely to “fail” the OGTT and thus be eligible for diabetes prevention interventions. In this analysis, we considered use of the MetS to guide screening for IGT. The MetS is a readily recognizable pre-diabetic condi-

tion. Recent clinical definitions have raised awareness of the syndrome, although how and why to use the syndrome in clinical practice is somewhat uncertain (35). In our analysis of >9,000 participants in four epidemiological studies, the MetS had excellent capacity to identify nondiabetic subjects likely to fail an OGTT. In particular, subjects with the MetS defined by IFG in combination with other traits had a substantially elevated probability of also having IGT. For instance, in our study samples, 61–93% of subjects with IFG, high triglycerides, and/or a large waist circumference failed an OGTT, whereas 62–87% without these traits had normal glucose tolerance. The MetS defined by trait combinations not including IFG were less useful for

identifying IGT. Nonspecific combinations of any two or any three traits (the MetS) were more prevalent than the syndrome based on IFG and so accounted for a greater proportion of IGT on a population-wide basis but conferred less risk to an individual than MetS based on IFG. Using AROC values as a guide to the value of prediction models, our results show that relatively simple trait identification (for instance, diagnosing IFG, high triglycerides, and/or a large waist circumference) had similar discriminatory capacity as more complex regression models including all risk factors, age, and sex. We also found that IFG, high triglycerides, and a large waist circumference were essentially similar predictors of IGT in the Caucasian, Mexican, and African-

American samples. Thus, our analysis demonstrates that clinical identification of the MetS, including IFG in particular, appears to be an excellent method to identify candidates for OGTT and diabetes prevention interventions.

It is not surprising that subjects with IFG as one of the MetS traits had a high risk of IGT (36), despite that in some cases IFG and IGT may represent different pre-diabetic phenotypes (37,38). The recent American Diabetes Association proposal to lower the threshold defining IFG to 5.6 mmol/l was intended, in part, to optimize the ability of IFG to predict future diabetes (31). However, our analysis does not suggest any obvious advantages of the new IFG criteria for detection of IGT. The “new” IFG is more common and so accounts for a greater proportion of IGT in the population, but the lower ORs and PPVs suggest that an individual with IFG of 5.6–6.9 mmol/l as one of the MetS traits is less likely to fail an OGTT than a person with IFG of 6.1–6.9 mmol/l and the MetS. Regardless of the definition of “impaired,” our analysis supports fasting glucose testing as a key step in screening for IGT. However, our data and screening data from the U.S., Canada, and Sweden all demonstrate that use of IFG alone is probably insufficient to accurately detect most cases of IGT (39–41). Combining IFG with other risk factors as clinical prediction rules can improve on the yield of IGT detection. In an analysis (the Third National Health and Nutrition Examination Survey), Nelson and Boyko (42) reported that IFG increased risk of IGT by sixfold; overall obesity (a BMI ≥ 25 kg/m²), Mexican-American ethnicity, older age, hypertension, and triglyceride levels ≥ 1.69 mmol/l were also independent risk factors. An 8-point prediction rule based on these variables had discriminatory capacity similar to that in our data for IFG plus hypertriglyceridemia or central obesity (AROC 0.74). Schmidt et al. (43) assessed detection of IFG, IGT, or clinically undetected diabetes in an analysis of Atherosclerosis Risk in Communities Study data. FPG ≥ 6.1 mmol/l alone detected only 28% of prevalent IFG/IGT in the sample. Lowering the “abnormal” FPG threshold to 5.6 mmol/l detected more (58%) IFG/IGT, but approximately one-half of “screen-positive” subjects had normal glycemia on OGTT. Adding to FPG ≥ 5.6 mmol/l, a “high-risk” score based on a clinical detection rule (using age, height,

Table 4—Multivariate prediction of IGT (2hPG ≥ 7.8 mmol/l) using traits of the MetS in FOS, SAHS, MCDS, and IRAS

	SAHS					IRAS		
	FOS Caucasian	Non-Hispanic Caucasian	Mexican American	MCDS Mexican	Non-Hispanic Caucasian	Mexican American	African American	
IFG (FPG 6.1–6.9 mmol/l)	6.41 (4.80–8.55)	9.13 (4.50–18.5)	7.46 (4.78–11.7)	12.9 (7.32–22.9)	3.19 (1.76–5.80)	5.56 (2.91–10.7)	10.8 (5.49–21.3)	
Large waist circumference (>102/88 cm, men/women)	1.35 (1.08–1.69)	2.81* (1.96–4.03)	1.92 (1.48–2.48)	1.50 (1.06–2.12)	3.99* (2.48–6.42)	1.81 (1.09–2.99)	2.63 (1.40–4.94)	
High TG (≥ 1.7 mmol/l)	2.31 (1.83–2.92)	1.64 (1.14–2.35)	1.53 (1.19–1.96)	2.37 (1.75–3.21)	1.85 (1.15–2.98)	2.38 (1.50–3.80)	1.10 (0.49–2.50)	
Low HDL (<1.0/1.16 mmol/l, men/women)	1.19 (0.95–1.51)	1.09 (0.76–1.57)	1.22 (0.94–1.58)	0.90 (0.54–1.52)	1.05 (0.67–1.65)	1.17 (0.72–1.91)	1.50 (0.79–2.82)	
High BP ($\geq 130/85$ mmHg or Rx)	1.78 (1.40–2.26)	1.41 (0.98–2.03)	1.98 (1.52–2.58)	1.64 (1.23–2.17)	1.15 (0.74–1.81)	1.21 (0.75–1.94)	1.79 (0.95–3.40)	
AROC								
Study's own function	0.793	0.759	0.761	0.712	0.747	0.772	0.834	
Using FOS function	—	0.735	0.746	0.708	0.717	0.77	0.818	
Calibration χ^2 statistic								
Study's own function	18.72	9.57	7.70	8.35	3.65	9.65	10.47	
Using FOS function	—	42.3	275.0	75.3	197.2	218.8	116.6	
After recalibration†	—	23.7	24.3	28.2	10.4	9.9	7.7	

Data are OR (95% CI). AROC, area under the receiver operating characteristic curve for the age-, sex-, and metabolic syndrome trait-adjusted logistic regression model predicting IGT, or χ^2 statistics; * $P < 0.0007$; †using the FOS model, with adjustment to the intercept for the study's own event rate and risk factor mean values.

Table 5—Association of IGT (2hPG \geq 7.8 mmol/l) with traits of the MetS in the FOS, SAHS, and MCDS, applying the American Diabetes Association (ADA) 2003 definition for IFG (FPG 5.6–6.9 mmol/l)

	FOS Caucasian							SAHS Non-Hispanic Caucasian							SAHS Mexican American						
	P(t)	OR	AROC	PPV	NPV	AR %	PAR %	P(t)	OR	AROC	PPV	NPV	AR %	PAR %	P(t)	OR	AROC	PPV	NPV	AR %	PAR %
IFG ADA 2003 (FPG 5.6–6.9 mmol/l)	0.29	4.71	0.760	0.30	0.92	74.0	45.0	0.14	3.79	0.700	0.37	0.87	66.0	21.0	0.19	5.24	0.740	0.51	0.83	67.0	28.0
IFG and high TG	0.12	5.65	0.750	0.42	0.89	75.0	27.0	0.06	4.80	0.680	0.45	0.86	69.0	11.0	0.11	5.07	0.710	0.54	0.80	64.0	16.0
IFG and large waist	0.14	4.41	0.740	0.38	0.89	71.0	26.0	0.08	5.44	0.690	0.47	0.87	72.0	16.0	0.13	5.00	0.720	0.55	0.81	66.0	20.0
IFG and high BP	0.18	4.30	0.750	0.36	0.90	73.0	33.0	0.06	4.18	0.670	0.45	0.86	68.0	11.0	0.08	7.02	0.720	0.64	0.80	69.0	15.0
IFG and low HDL-C	0.13	4.08	0.740	0.36	0.89	69.0	22.0	0.08	3.65	0.690	0.38	0.86	64.0	13.0	0.13	5.15	0.730	0.53	0.81	64.0	19.0
Any two traits	0.53	5.48	0.760	0.23	0.95	80.0	68.0	0.52	3.23	0.700	0.23	0.92	66.0	50.0	0.60	3.84	0.730	0.32	0.90	69.0	57.0
IFG, high TG, high BP	0.09	5.00	0.730	0.44	0.88	73.0	20.0	0.03	6.82	0.660	0.57	0.85	74.0	7.0	0.05	6.50	0.700	0.64	0.79	67.0	10.0
IFG, high TG, low HDL-C	0.08	5.36	0.740	0.44	0.88	73.0	18.0	0.05	4.25	0.670	0.43	0.86	66.0	9.0	0.08	5.28	0.710	0.57	0.80	64.0	13.0
IFG, high TG, large waist	0.07	5.09	0.730	0.44	0.88	73.0	16.0	0.04	6.91	0.670	0.54	0.86	74.0	10.0	0.07	4.41	0.700	0.55	0.79	62.0	11.0
IFG, large waist, low HDL-C	0.07	4.50	0.720	0.42	0.88	71.0	15.0	0.05	5.45	0.680	0.48	0.86	70.0	11.0	0.09	4.92	0.710	0.56	0.80	64.0	14.0
IFG, large waist, high BP	0.10	4.29	0.730	0.40	0.88	71.0	20.0	0.03	6.80	0.660	0.57	0.85	74.0	8.0	0.05	6.24	0.700	0.65	0.79	68.0	10.0
IFG, low HDL-C, high BP	0.09	3.83	0.720	0.39	0.88	69.0	16.0	0.04	4.34	0.660	0.47	0.85	68.0	7.0	0.06	6.68	0.710	0.63	0.79	67.0	11.0
Any three traits (MetS)	0.31	4.49	0.770	0.30	0.92	74.0	48.0	0.27	3.89	0.720	0.31	0.90	67.0	35.0	0.33	3.50	0.730	0.41	0.85	63.0	36.0
OR, IFG ADA 2003* (95% CI)	3.89 (3.12–4.86)			3.10 (2.08–4.62)			4.24 (3.21–5.59)														
AROC†	0.801			0.754			0.773														

For abbreviations, see footnote to Table 2. *OR (95% CI) for IFG predicting IGT in a model including age, sex, IFG, fasting triglycerides, waist circumference, blood pressure, and HDL cholesterol. †AROC using the study's own function.

weight, parental history of diabetes, diagnosed hypertension, systolic blood pressure, HDL cholesterol, and triglycerides) increased the detection rate to 58% of prevalent IFG/IGT. Administering an OGTT to this latter sample reduced to 29% the “true-positive” rate of IFG/IGT/diabetes. In these data, as in our study samples, FPG and fasting triglycerides were the two traits offering greatest predictive ability. Based on these analyses, we conclude that use of a fasting glucose sample plus one or two additional traits of the MetS to screen for IGT may be as useful, and substantially simpler, than using sophisticated clinical prediction rules.

Our analysis was predicated on the idea that an OGTT is needed for evidence-based translation of diabetes prevention trials. However, some authors have argued that individuals at high risk of diabetes are better identified with standard diabetes risk factors and that an OGTT may not be needed. In an analysis of SAHS data, Stern, Williams, and Haffner (18) reported that for prediction of 7.5-year incidence of type 2 diabetes, the AROC for a multivariable model including FPG, systolic blood pressure, HDL cholesterol, BMI, and a family history of diabetes was significantly ($P < 0.001$) greater than the AROC for the 2hPG level alone (0.843 vs. 0.775). Adding 2hPG to the prediction model increased the

AROC, but only from 0.843 to 0.857. This strategy is consistent with the general concept underlying the MetS that identification of elevated cardiovascular disease risk factors identifies people at elevated risk of type 2 diabetes. Furthermore, the NCEP ATP III recommends that people with adverse levels of metabolic disease risk factors should be prescribed therapeutic lifestyle interventions similar to those used in recent diabetes prevention trials, regardless of their glucose tolerance status. Thus, whether an OGTT is needed to proceed with implementing diabetes prevention strategies is an open question.

An OGTT might not be necessary for everyone with elevated metabolic risk factors, particularly as aggressive lifestyle interventions are already indicated. Indeed, treatment and prevention of obesity alone would have a substantial impact on diabetes risk in the population. Burke et al.(44) recently estimated that preventing development of overweight would result in a 62–74% reduction in the incidence of type 2 diabetes in Mexican Americans and non-Hispanic Caucasians. Preventing the entire population from gaining, on average, 1 BMI unit would result in a reduction in incidence of type 2 diabetes by ~13%. In addition, medical therapy of obesity with orlistat has recently been shown to reduce by ~50% the risk of type 2 diabetes in obese patients (45). Al-

though pharmaceutical therapy for medical obesity is readily defensible, therapy with metformin, acarbose, or thiazolidinediones to prevent diabetes in otherwise healthy individuals with IGT is a more complex issue. The risk/benefit ratio for long-term use of these drugs in individuals with subdiabetic glycemic levels is not known. The argument can be made that an OGTT would be indicated to establish IGT before long-term medical therapy of asymptomatic glucose intolerance. In addition, our data show that performing an OGTT will pick up 2–10% additional subjects with otherwise undetectable diabetes who warrant diabetes-specific interventions.

Our analysis has some limitations. We compared risk factor categories across four different studies that used generally similar assessment methods, but some methodological variation could have introduced small differences in risk factor distributions. We based our analysis on only one OGTT, which likely resulted in some misclassification by glucose tolerance status and may have inflated the prevalence of IGT but weakened associations with MetS traits. In clinical practice, however, most patients will likely undergo serial screening and eventually be classified correctly. Also, our outcome was not strictly “IGT,” as we included 2hPG \geq 11.1 mmol/l in the definition.

Table 5—Continued

MCDS Mexican														IRAS																	
														Non-Hispanic Caucasian						Mexican American						African American					
P(t)	OR	AROC	PPV	NPV	AR %	PAR %	P(t)	OR	AROC	PPV	NPV	AR %	PAR %	P(t)	OR	AROC	PPV	NPV	AR %	PAR %	P(t)	OR	AROC	PPV	NPV	AR %	PAR %				
0.10	10.25	0.710	0.57	0.89	81.0	30.0	0.44	4.63	0.730	0.54	0.77	57.0	—	0.42	5.19	0.750	0.63	0.74	58.0	—	0.53	12.33	0.810	0.63	0.88	81.0	—				
0.07	11.97	0.700	0.63	0.88	81.0	24.0	0.14	5.47	0.690	0.69	0.68	54.0	—	0.22	4.57	0.710	0.68	0.66	50.0	—	0.09	5.17	0.680	0.74	0.64	52.0	—				
0.07	9.29	0.670	0.59	0.88	79.0	21.0	0.18	9.19	0.730	0.78	0.72	64.0	—	0.20	5.65	0.700	0.75	0.67	56.0	—	0.24	8.29	0.760	0.75	0.72	63.0	—				
0.04	13.06	0.660	0.70	0.87	81.0	15.0	0.23	3.49	0.670	0.59	0.70	49.0	—	0.23	3.33	0.690	0.65	0.66	47.0	—	0.36	6.14	0.770	0.67	0.77	65.0	—				
0.10	9.59	0.710	0.57	0.89	80.0	27.0	0.23	4.30	0.700	0.61	0.71	52.0	—	0.28	4.09	0.710	0.65	0.68	50.0	—	0.22	4.78	0.710	0.66	0.69	52.0	—				
0.81	3.90	0.640	0.18	0.95	74.0	70.0	0.61	3.50	0.700	0.47	0.79	55.0	—	0.66	5.81	0.740	0.54	0.84	70.0	—	0.65	4.89	0.720	0.51	0.83	66.0	—				
0.03	16.80	0.660	0.75	0.86	81.0	12.0	0.08	4.63	0.650	0.69	0.66	50.0	—	0.13	3.82	0.680	0.69	0.63	46.0	—	0.05	4.51	0.660	0.75	0.63	51.0	—				
0.07	11.45	0.700	0.63	0.88	80.0	22.0	0.09	6.45	0.670	0.75	0.67	56.0	—	0.18	4.38	0.700	0.69	0.65	49.0	—	0.06	7.50	0.670	0.79	0.64	54.0	—				
0.05	10.14	0.660	0.63	0.87	79.0	16.0	0.07	6.48	0.660	0.77	0.66	56.0	—	0.11	3.99	0.670	0.70	0.62	46.0	—	0.05	10.19	0.670	0.87	0.63	58.0	—				
0.07	8.88	0.670	0.58	0.87	78.0	19.0	0.11	8.70	0.700	0.79	0.69	60.0	—	0.15	4.86	0.680	0.73	0.64	51.0	—	0.12	7.06	0.700	0.75	0.66	54.0	—				
0.03	10.53	0.640	0.67	0.86	79.0	10.0	0.12	8.29	0.680	0.80	0.69	61.0	—	0.12	3.74	0.670	0.71	0.63	47.0	—	0.17	6.30	0.730	0.76	0.68	58.0	—				
0.04	13.33	0.660	0.70	0.86	81.0	13.0	0.11	3.59	0.650	0.64	0.67	48.0	—	0.14	2.84	0.660	0.64	0.62	41.0	—	0.14	8.14	0.720	0.79	0.68	59.0	—				
0.45	3.71	0.690	0.25	0.92	69.0	50.0	0.33	5.62	0.740	0.64	0.76	63.0	—	0.42	3.63	0.720	0.60	0.72	53.0	—	0.33	5.66	0.750	0.66	0.74	61.0	—				
		9.3 (6.72–12.9)							3.96 (2.49–6.30)						4.00 (2.48–6.46)							10.5 (5.45–20.1)									
		0.755							0.776						0.778							0.836									

This slightly increased the prevalence of “IGT” and of PPVs associated with the MetS and identified subjects perhaps beyond need of “diabetes prevention.” However, from the practical perspective, we have tried to take in this analysis subjects with postchallenge diabetes who would not be discovered unless they underwent OGTT, and thus identifying them for appropriate intervention is an inseparable part of the rationale behind using the MetS as a strategy to select subjects for OGTT. In any case, use of 2hPG ≥ 7.8 mmol/l to define IGT did not materially alter the conclusions of the study. Finally, the small number of African-American subjects in the analysis limited the confidence with which inter-race/ethnicity comparisons could be made.

In summary, we examined the value of the MetS and its constituent traits to identify subjects likely to have IGT (or undiagnosed diabetic postchallenge hyperglycemia) on subsequent OGTT. The MetS, especially with IFG as one of the diagnostic traits, is an excellent discriminator of subjects likely to fail an OGTT. The ability of IFG in combination with one or two other traits (especially a large waist circumference or a triglyceride level ≥ 1.7 mmol/l) to detect IGT compares favorably with more complex strategies using regression-based clinical prediction rules. Our data suggest that subjects with the MetS should be considered for an OGTT and for subsequent evidence-

based interventions to prevent progression to type 2 diabetes and its devastating and costly long-term complications.

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References

- Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ: Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 24:1936–1940, 2001
- Hogan P, Dall T, Nikolov P: Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 26:917–932, 2003
- Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in

people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997

- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
- Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KM: Estimated number of adults with pre-diabetes in the U.S. in 2000: opportunities for prevention. *Diabetes Care* 26:645–649, 2003
- Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications: Part 1. Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
- Charles MA, Fontbonne A, Thibault N, Warnet JM, Rosselin GE, Eschwege E: Risk factors for NIDDM in white population: Paris prospective study. *Diabetes* 40:796–799, 1991
- de Vegt F, Dekker JM, Jager A, Hienkens

- E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 285:2109–2113, 2001
11. Vaccaro O, Ruffa G, Imperatore G, Iovino V, Rivellese AA, Riccardi G: Risk of diabetes in the new diagnostic category of impaired fasting glucose: a prospective analysis. *Diabetes Care* 22:1490–1493, 1999
 12. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 23:1108–1112, 2000
 13. DECODE Study Group: Consequences of the new diagnostic criteria for diabetes in older men and women: DECODE Study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe). *Diabetes Care* 22:1667–1671, 1999
 14. Shaw JE, de Courten M, Boyko EJ, Zimmet PZ: Impact of new diagnostic criteria for diabetes on different populations. *Diabetes Care* 22:762–766, 1999
 15. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes* 20:1183–1197, 1997
 16. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
 17. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of diabetes? *JAMA* 263:2893–2898, 1990
 18. Stern MP, Williams K, Haffner SM: Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med* 136:575–581, 2002
 19. Kannel WB, Feinleib M, McNamara JR, Garrison RJ, Castelli WP: An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol* 110:281–290, 1979
 20. Meigs JB, Nathan DM, Wilson PWF, Cupples LA, Singer DE: Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: the Framingham Offspring Study. *Ann Intern Med* 128:524–533, 1998
 21. McNamara JR, Schaefer EJ: Automated enzymatic standardized lipid analyses for plasma and lipid lipoprotein fractions. *Clin Chim Acta* 166:1–8, 1987
 22. Warnick GR, Benderson J, Albers JJ: Dextran sulfate-magnesium precipitation procedure for quantitation of high-density lipoprotein cholesterol. *Clin Chem* 28:1379–1382, 1982
 23. Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ: Sex differences in the effect of sociocultural status on diabetes and cardiovascular risk factors in Mexican-Americans: the San Antonio Heart Study. *Am J Epidemiol* 120:834–851, 1984
 24. Stern MP, Patterson JK, Haffner SM, Hazuda HP, Mitchell BD: Lack of awareness and treatment of hyperlipidemia in type II diabetes in a community survey. *JAMA* 262:360–364, 1989
 25. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 159:1450–1456, 1999
 26. Haffner SM, Gonzalez C, Mykkanen L, Stern M: Total immunoreactive proinsulin, immunoreactive insulin and specific insulin in relation to conversion to NIDDM: the Mexico City Diabetes Study. *Diabetologia* 40:830–837, 1997
 27. Burke JP, Williams K, Haffner SM, Villalpando CG, Stern MP: Elevated incidence of type 2 diabetes in San Antonio, Texas, compared with that of Mexico City, Mexico. *Diabetes Care* 24:1573–1578, 2001
 28. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, et al.: The insulin resistance atherosclerosis study (IRAS) objectives, design, and recruitment results. *Ann Epidemiol* 5:464–472, 1995
 29. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenknecht LE, Bergman RN: Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45:742–748, 1996
 30. National Cholesterol Education Program: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
 31. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
 32. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 286:180–187, 2001
 33. Meigs JB, Wilson PWF, Nathan DM, D'Agostino RB, Williams K, Haffner SM: Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 52:2160–2167, 2003
 34. National Institutes of Health: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obes Res* 6 (Suppl. 2):51S–209S, 1998
 35. Meigs JB: The metabolic syndrome. *BMJ* 327:61–62, 2003
 36. DECODE Study Group: Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes: reanalysis of European epidemiological data. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. *BMJ* 317:371–375, 1998
 37. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R: The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 52:1475–1484, 2003
 38. Carnevale Schianca GP, Rossi A, Sainaghi PP, Maduli E, Bartoli E: The significance of impaired fasting glucose versus impaired glucose tolerance: importance of insulin secretion and resistance. *Diabetes Care* 26:1333–1337, 2003
 39. Saydah SH, Byrd-Holt D, Harris MI: Projected impact of implementing the results of the diabetes prevention program in the U.S. population. *Diabetes Care* 25:1940–1945, 2002
 40. Anand SS, Razak F, Vuksan V, Gerstein HC, Malmberg K, Yi Q, Teo KK, Yusuf S: Diagnostic strategies to detect glucose intolerance in a multiethnic population. *Diabetes Care* 26:290–296, 2003
 41. Lindahl B, Weinehall L, Asplund K, Hallmans G: Screening for impaired glucose tolerance: results from a population-based study in 21,057 individuals. *Diabetes Care* 22:1988–1992, 1999
 42. Nelson KM, Boyko EJ: Predicting impaired glucose tolerance using common clinical information: data from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 26:2058–2062, 2003
 43. Schmidt MI, Duncan BB, Vigo A, Pankow J, Ballantyne CM, Couper D, Brancati F, Folsom AR: Detection of undiagnosed diabetes and other hyperglycemia states: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 26:1338–1343, 2003
 44. Burke JP, Williams K, Narayan KM, Leibson C, Haffner SM, Stern MP: A population perspective on diabetes prevention: whom should we target for preventing weight gain? *Diabetes Care* 26:1999–2004, 2003
 45. Heymsfield SB, Segal KR, Hauptman J, Lucas CP, Boldrin MN, Rissanen A, Wilding JP, Sjostrom L: Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 160:1321–1326, 2000