

Identifying Individuals at High Risk for Diabetes

The Atherosclerosis Risk in Communities study

MARIA INÊS SCHMIDT, MD, PHD^{1,2}
 BRUCE B. DUNCAN, MD, PHD^{1,2}
 HEEJUNG BANG, PHD³
 JAMES S. PANKOW, PHD⁴
 CHRISTIE M. BALLANTYNE, MD⁵

SHERITA H. GOLDEN, MD, MHS⁶
 AARON R. FOLSOM, MD⁴
 LLOYD E. CHAMBLESS, PHD³
 FOR THE ATHEROSCLEROSIS RISK IN
 COMMUNITIES INVESTIGATORS

OBJECTIVE — To develop and evaluate clinical rules to predict risk for diabetes in middle-aged adults.

RESEARCH DESIGN AND METHODS — The Atherosclerosis Risk in Communities is a cohort study conducted from 1987–1989 to 1996–1998. We studied 7,915 participants 45–64 years of age, free of diabetes at baseline, and ascertained 1,292 incident cases of diabetes by clinical diagnosis or oral glucose tolerance testing.

RESULTS — We derived risk functions to predict diabetes using logistic regression in a random half of the sample. Rules based on these risk functions were evaluated in the other half. A risk function based on waist, height, hypertension, blood pressure, family history of diabetes, ethnicity, and age was performed similarly to one based on fasting glucose (area under the receiver-operating characteristic curve [AUC] 0.71 and 0.74, respectively; $P = 0.2$). Risk functions composed of the clinical variables plus fasting glucose (AUC 0.78) and additionally including triglycerides and HDL cholesterol (AUC 0.80) performed better ($P < 0.001$). Evaluation of scores based on the metabolic syndrome as defined by the National Cholesterol Education Program or with slight variations showed AUCs of 0.75 and 0.78, respectively. Rules based on all these approaches, while identifying 20–56% of the sample as screen positive, achieved sensitivities of 40–87% and specificities of 50–86%.

CONCLUSIONS — Rules derived from clinical information, alone or combined with simple laboratory measures, can characterize degrees of diabetes risk in middle-aged adults, permitting preventive actions of appropriate intensity. Rules based on the metabolic syndrome are reasonable alternatives to rules derived from risk functions.

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Prevention of diabetes and its associated burden has become a major health priority worldwide (1). Recent clinical trials demonstrate that lifestyle (2–4) and pharmaceutical (2,5,6) interventions in individuals with impaired glucose tolerance (IGT) can prevent the development of diabetes, providing a rationale for the identification of high-risk subjects so as to institute early lifestyle interventions.

Because these trials focused primarily on individuals with IGT, an oral glucose tolerance test (OGTT) was required to identify individuals meriting intervention. The inconveniences and costs associated with this test (7) have stimulated the development of simple rules involving readily available clinical information capable of predicting diabetes with equal or better diagnostic properties than IGT. Currently reported investigations are limited to Mexican Americans and non-Hispanic whites (8), Japanese Americans (9), and Finns (10).

The purpose of this study is to develop and evaluate rules to predict high risk of developing diabetes in middle-aged, white, and African-American adults using readily available clinical information.

RESEARCH DESIGN AND METHODS

In 1987–1989, the Atherosclerosis Risk in Communities (ARIC) study recruited a population-based cohort of 15,792 men and women 45–64 years of age from four U.S. communities (11). Human subjects research review committees approved the study, and all participants gave written consent. Follow-up visits, ~3 years apart, were conducted in 1990–1992, 1993–1995, and 1996–1998.

We excluded 2,018 individuals who at baseline had diabetes on the basis of clinical diagnosis, diabetes medication use, or fasting glucose ≥ 7.0 mmol/l (an OGTT was not performed at baseline), 95 from underrepresented minority groups, 210 not fasting for at least 8 h, 1,696 with missing information on risk factors at

From the ¹Graduate Studies Program in Epidemiology, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; the ²Department of Epidemiology, School of Public Health at Chapel Hill, University of North Carolina, Chapel Hill, North Carolina; the ³Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, North Carolina; the ⁴Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota; the ⁵Department of Medicine, Baylor College of Medicine, Houston, Texas; and the ⁶Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address correspondence and reprint requests to Maria Inês Schmidt, School of Medicine, UFRGS R. Ramiro Barcelos, 2600/414 Porto Alegre, RS 90035-003, Brazil. E-mail: mischmidt@orion.ufrgs.br.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; AUC, area under the receiver-operating characteristic curve; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; ROC, receiver-operating characteristic.

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

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baseline, 3,834 who had no follow-up or incomplete information at the end of the study to ascertain diabetes, and 24 who had temporally inconsistent reporting of a diagnosis of diabetes across visits, thus leaving 7,915 participants for the analyses.

We assessed diabetes and hypertension medication use, smoking, and parental history of diabetes (in either parent) by interview and obtained physical measures with participants fasting and with an empty bladder. BMI was calculated as weight/height² (kg/m²), and obesity was defined as a BMI ≥ 30 kg/m². Waist girth was measured at the umbilical level. Blood pressure was determined as the mean of two standardized measurements.

All analytes were determined at central laboratories according to standard protocols: plasma glucose by a hexokinase assay, insulin by radioimmunoassay (¹²⁵I insulin kit; Cambridge Medical Diagnosis, Billerica, MA), and triglycerides and HDL cholesterol by enzymatic methods (12).

We defined incident diabetes by an OGTT (fasting glucose ≥ 7.0 mmol/l or a 2-h glucose ≥ 11.1 mmol/l) at the end of the follow-up (1996–1998) or as a report of clinical diagnosis or treatment for diabetes during the follow-up period (13,14).

In consonance with the National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition of the metabolic syndrome (15), we defined central obesity as a waist circumference >88 cm (35 in) for women and >102 cm (40 in) for men; high triglycerides as ≥ 150 mg/dl (1.70 mmol/l); low HDL cholesterol as <40 mg/dl (1.03 mmol/l) for men and <50 mg/dl (1.29 mmol/l) for women; impaired fasting glucose as a fasting value from 6.1 to 6.9 mmol/l as well as, following recent American Diabetes Association recommendations (16), from 5.6 to 6.9 mmol/l; and raised blood pressure as $\geq 130/85$ mmHg or use of medication for hypertension.

We produced risk functions for detecting incident diabetes on a randomly selected half of the sample (training sample) using logistic regression models. Risk factors considered were sex, ethnicity, parental history of diabetes, use of medication for hypertension, height, age, various measures of obesity (waist, weight, BMI, waist-to-hip ratio, each investigated one at a time), systolic blood pressure, fasting glucose, HDL cholesterol, triglycerides,

and fasting insulin. Continuous variables were examined with their squared terms. Models were built by including, first, easily obtained clinical variables, leaving those requiring laboratory determination for a second phase. Starting with variables that predicted incident diabetes in univariate models, we constructed multivariable models in a forward manner, eventually including all variables whose addition produced an increment of at least 0.005 in the area under the receiver-operating characteristic (ROC) curve (AUC) (17).

Once best models were defined, we evaluated their diagnostic properties on the other random half of the sample (testing sample). To do so, we first estimated each subject's probability of developing diabetes based on the derived risk functions. We next established rules to characterize differing degrees of risk based on cut points of these probabilities. These cut points were defined by fixing proportions (20, 30, 40, and 50%) of the testing sample that would be deemed screen positive. We then evaluated the risk functions and their derived rules in terms of AUC, fraction of total incident cases identified (sensitivity), specificity, and positive and negative predictive values.

We also examined similar diagnostic properties of rules based on the NCEP Adult Treatment Panel III metabolic syndrome definition and variations of it in the testing sample. We estimated 95% CIs for the AUCs, sensitivity, specificity, and predictive values using 500 bootstrap samples (18). All analyses were performed with SAS software (SAS Institute, Cary, NC).

RESULTS— At baseline, 56% of the 7,915 individuals studied were women, 85% were white, 27% were hypertensive, and 20% were current smokers. Median and interquartile range for various characteristics were as follows: age 54 years (49–59); BMI 26.6 kg/m² (23.7–30.1); waist, women, 93 cm (84–103); waist, men, 97 cm (91–104); height 168 cm (161–175); systolic blood pressure 120 mmHg (108–133); fasting glucose 5.44 mmol/l (5.11–5.83). Comparing these characteristics with those of the 5,764 subjects excluded, the only characteristics suggesting possible important systematic differences were a greater percentage of African Americans, smokers, and hypertensive subjects among those excluded. Only 2% of the final

sample was taking cholesterol-lowering medication.

We ascertained 1,292 cases of incident diabetes: 189 (cumulative incidence of 23.6%) among African-American women, 93 (22.5%) among African-American men, 532 (14.6%) among white women, and 478 (15.7%) among white men. Of these cases, 387 (30%) were ascertained by self-report of clinical diagnosis or medication use for diabetes. Independent of this ascertainment, the OGTT identified 1,156 (89%) case subjects, 317 (24%) by fasting glucose alone, 511 (40%) by 2-h glucose alone, and 328 (25%) by both criteria. Of total case subjects, all except 15 who were ascertained by self-report of diabetes at ARIC interim visits were present at the last follow-up visit.

We initially defined two models: one including only clinically detectable elements not requiring laboratory evaluation and the other including only fasting glucose. Next, we defined two further models. The first combined elements of the two initial models and the second additionally contained HDL cholesterol and triglycerides. Neither BMI nor fasting insulin was included in these models because the additional contribution to the AUC, although statistically significant, was minimal for each. Models generating risk functions separately for African Americans and whites had generally similar β coefficients and are not reported.

The diagnostic properties of the risk functions were next evaluated in the testing sample. Figure 1A shows the percent of incident diabetes case subjects in each decile of estimated risk. Risk functions including laboratory measurements provided important risk stratification: 52% of case subjects were distributed in the two highest deciles of risk, and 15% were distributed in the five lowest deciles. Figure 1B illustrates the fraction of individuals in each decile of estimated risk who developed diabetes (positive predictive value) for each model. Participants classified in the 9th and 10th deciles of estimated risk by the model including lipids had, in fact, a 33 and 52% risk of developing diabetes, respectively; among individuals in intermediate-risk categories (deciles 6–8), risk ranged from 13 to 24%. The other risk functions performed slightly worse, more so for that composed only of clinical variables.

Table 1 presents diagnostic proper-

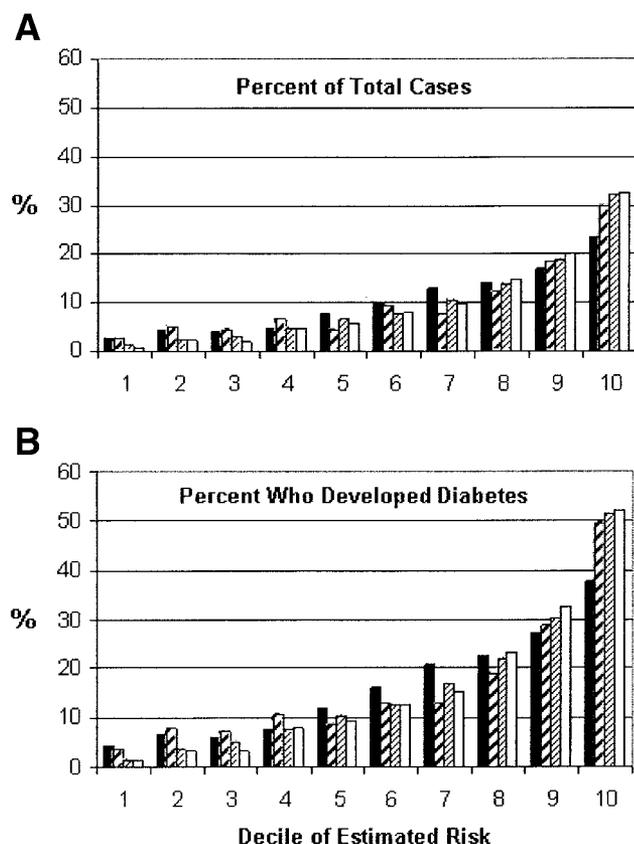


Figure 1—A: Percentage of incident cases of diabetes detected during the 9 years of follow-up in each decile of estimated risk. Risks were estimated from models (see equations in the footnote of Table 1) based only on readily available clinical information (solid bars), only on fasting glucose (dark hatched bars), on clinical information plus fasting glucose (light hatched bars), and on these elements plus HDL cholesterol and triglycerides (open bars). B: Percentage who actually developed diabetes during the 9 years of follow-up (positive predictive value), according to decile of estimated risk. Risks were estimated from models (see equations in the footnote of Table 1) based only on readily available clinical information (solid bars), only on fasting glucose (dark hatched bars), on clinical information plus fasting glucose (light hatched bars), and on these elements plus HDL cholesterol and triglycerides (open bars).

ties for each risk function, displaying rules based on cut points, chosen to permit the percentage of the population identified as at risk to vary from 20 to 50%.

Although differences are small, rules based on risk functions including laboratory measurements performed generally better, as reflected in the estimated AUCs for these models (Table 1). Predictive ability of the clinical variable only and fasting glucose only models was not significantly different (AUC 0.71 vs. 0.74, $P = 0.2$). Compared with the clinical variable only model, the model combining clinical elements with fasting glucose was more predictive (AUC 0.78, $P < 0.001$) and that including lipids was the best predictor (AUC 0.80, $P < 0.001$).

Table 2 shows the properties of rules

based on the presence of elements of the metabolic syndrome. Rules attributing equal weights for each element of the metabolic syndrome produced somewhat less desirable diagnostic properties than rules based on the risk function including lipids (Table 1). For instance, the presence of the metabolic syndrome (three or more abnormalities) labeled 23% as positive and identified 50% of future cases of diabetes (sensitivity), whereas a rule derived from the risk function including lipids, labeling as high risk a slightly lower sample fraction (20%), correctly identified slightly more (52%) future cases. The rule with NCEP cut points also showed less overall predictive capacity than the risk function including lipids (AUC 0.75 vs. 0.80, $P < 0.001$).

Lowering the NCEP cut point for fast-

ing glucose (≥ 5.6 mmol/l) in the definition of the metabolic syndrome did not improve overall predictability (AUC = 0.75), but produced rules labeling the greater fraction of the sample as at high risk, and as such, had higher sensitivity and lower specificity.

Also seen in Table 2 are the diagnostic characteristics of rules based on an alternative metabolic syndrome approach, derived from rounding of the β coefficients of an all-categorical variable model. We assigned 1 point for the presence of each element of the metabolic syndrome (except impaired fasting glucose) present, 1 additional point for obesity (BMI ≥ 30 kg/m²), and 2 points for a fasting glucose ≥ 5.6 mmol/l (or 5 points when ≥ 6.1 mmol/l). Rules based on this approach performed slightly better. For example, a score ≥ 5 , labeling 22% of participants as at high risk, identified 54% of future cases of diabetes; and a score ≥ 3 , labeling 46% of participants as high risk, identified 81% of future cases of diabetes. The AUC for this approach (0.78) was greater than that obtained for the original NCEP rule (0.75, $P < 0.001$).

When the best risk function, that including lipids, was evaluated in sex and ethnicity strata, AUCs were 0.79 (95% CI 0.76–0.82) for men, 0.81 (0.78–0.83) for women, 0.80 (0.78–0.82) for whites, and 0.76 (0.71–0.80) for African Americans. Additional analyses showed that developing a risk function containing lipids on a training sample using only African-American participants did not improve its performance in this ethnic group in the testing sample (data not shown).

Diagnostic properties were better when the analysis was based only on cases ascertained by clinical diagnosis or treatment. For example, the AUC for the risk function including lipids increased from 0.80 to 0.87; that based only on clinical variables increased from 0.71 to 0.78. Finally, we tested in whites a clinical score developed in the San Antonio Heart Study (8) composed of age, sex, family history of diabetes, BMI, HDL cholesterol, and hypertension and found an AUC of 0.80.

CONCLUSIONS— Clinical trials demonstrate that high-risk individuals, defined as having IGT, can reduce their risk of diabetes by more than half when offered a well-structured intensive lifestyle modification program (2,3). Diagnosing IGT requires an OGTT, a test of

Table 1—Diagnostic characteristics in the testing sample of rules predicting risk of incident diabetes in the ARIC study

	%+	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Models and rules					
Clinical information only			AUC = 0.71 (0.69–0.73)		
Pr(DM)					
≥0.23	20	40 (37–44)	84 (83–85)	32 (29–36)	88 (87–89)
≥0.19	30	54 (51–58)	75 (74–75)	29 (27–32)	90 (88–91)
≥0.16	40	67 (64–71)	65 (64–66)	27 (25–30)	91 (90–92)
≥0.14	50	77 (74–80)	55 (54–56)	25 (23–27)	93 (91–94)
Fasting glucose only (mmol/l)			AUC = 0.74 (0.71–0.76)		
Pr(DM)					
≥0.24 (≥5.88)	20	50 (46–53)	84 (83–86)	38 (35–42)	90 (88–91)
≥0.19 (≥5.72)	30	60 (57–64)	76 (74–76)	32 (29–35)	91 (90–92)
≥0.15 (≥5.55)	40	70 (66–73)	63 (62–66)	27 (25–29)	92 (90–93)
≥0.13 (≥5.44)	50	77 (74–80)	54 (52–55)	24 (22–26)	92 (91–94)
Clinical + glucose			AUC = 0.78 (0.76–0.80)		
Pr(DM)					
≥0.26	20	51 (47–54)	86 (85–87)	41 (37–45)	90 (89–91)
≥0.18	30	65 (61–68)	77 (76–77)	35 (31–37)	92 (91–93)
≥0.14	40	75 (72–78)	67 (66–67)	30 (28–32)	93 (92–94)
≥0.11	50	83 (80–85)	56 (56–57)	27 (24–28)	94 (93–95)
Clinical + glucose + lipids			AUC = 0.80 (0.78–0.82)		
Pr(DM)					
≥0.26	20	52 (49–56)	86 (85–87)	42 (39–46)	90 (89–91)
≥0.18	30	67 (64–70)	77 (76–78)	36 (33–39)	92 (91–93)
≥0.14	40	77 (73–80)	67 (66–68)	31 (29–33)	94 (93–95)
≥0.10	50	85 (81–88)	57 (56–57)	27 (25–29)	95 (94–96)

Data in parentheses are 95% CIs. %+, percentage of sample identified as screen positive by the detection rule; Pr(DM), probability of developing diabetes, derived from the prediction model, used as the high-risk cut point. The following are parameter estimates for the models estimating the probability of developing diabetes over the 9-year follow-up period:

$$\text{Pr(DM)} = 1/(1 + e^{-x}), \text{ where } x =$$

Clinical variables only model: $-7.3359 + 0.0271 \times \text{age (years)} + 0.2295 \times \text{black} + 0.5463 \times \text{parental history of diabetes} + 0.0161 \times \text{systolic blood pressure (mmHg)} + 0.0412 \times \text{waist (cm)} - 0.0115 \times \text{height (cm)}$.

Fasting glucose only: $-11.7303 + 1.7996 \times \text{fasting glucose (mmol/l)}$.

Note: When using traditional units, the coefficient for fasting glucose (mg/dl) is 0.0999.

Clinical variables plus fasting glucose: $-12.2555 + 0.0168 \times \text{age (years)} + 0.2631 \times \text{black} + 0.5088 \times \text{parental history of diabetes} + 1.6445 \times \text{fasting glucose (mmol/l)} + 0.0120 \times \text{systolic blood pressure (mmHg)} + 0.0328 \times \text{waist (cm)} - 0.0261 \times \text{height (cm)}$.

Note: When using traditional units, the coefficient for fasting glucose (mg/dl) is 0.0913.

Clinical variables plus fasting glucose and lipids: $-9.9808 + 0.0173 \times \text{age (years)} + 0.4433 \times \text{black} + 0.4981 \times \text{parental history of diabetes} + 1.5849 \times \text{fasting glucose (mmol/l)} + 0.0111 \times \text{systolic blood pressure (mmHg)} + 0.0273 \times \text{waist (cm)} - 0.0326 \times \text{height (cm)} - 0.4718 \times \text{HDL cholesterol (mmol/l)} + 0.2420 \times \text{triglycerides (mmol/l)}$.

Note: When using traditional units, the coefficient is 0.0880 for fasting glucose (mg/dl), 0.0122 for HDL cholesterol (mg/dl), and 0.00271 for triglycerides (mg/dl).

Black = 1 if African American, 0 if white, and parental history of diabetes = 1 if at least one parent has diabetes or 0 if not.

high specificity (92%) but low sensitivity (52%) in the prediction of diabetes (8).

Our results indicate that a rule defining high risk (9-year probability of developing diabetes ≥26%) based on the risk function composed of multiple variables including lipids had similar diagnostic properties (sensitivity 52% and specificity 86%, respectively), labeling 20% of the sample as high risk. These properties are generally consistent with those previously reported for similarly constructed rules (8,9). Slight differences between results of the three studies are probably accounted

for by differences in population characteristics such as age and ethnicity, duration of follow-up, and diabetes definition.

Of note is that rules derived from other risk functions (Table 1) and from various clinical scores based on the metabolic syndrome definitions (Table 2) had similar, though somewhat poorer, diagnostic properties at cut points labeling a similar fraction (~20%) as positive.

Although the best diagnostic properties found here were those derived from a risk function including lipid variables

(AUC 0.80), the gain is small compared with those derived from a risk function without lipids (AUC 0.78) and, depending on the setting, may not justify the increased resources needed for the lipid measures. In settings in which HDL cholesterol and triglyceride measurements are readily available, rules based on the metabolic syndrome definition (Table 2) are valid, although slightly less predictive, alternatives to rules based on risk functions including these variables. Similar findings have been described recently (19). Yet, for those who prefer to classify

Table 2—Diagnostic characteristics in the testing sample of metabolic syndrome–based rules in predicting high risk of diabetes in the ARIC study

	%+	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Metabolic syndrome rules					
NCEP (IFG ≥ 6.1 mmol)*					
AUC = 0.75 (0.73–0.77)					
≥ 3	23	50 (47–55)	82 (81–84)	36 (33–39)	90 (89–91)
≥ 2	47	80 (77–83)	59 (58–61)	27 (25–29)	94 (93–95)
NCEP (IFG ≥ 5.6 mmol)					
AUC = 0.75 (0.73–0.77)					
≥ 3	32	64 (59–66)	74 (74–77)	32 (30–36)	91 (90–92)
≥ 2	56	87 (83–89)	50 (50–53)	25 (24–27)	95 (94–96)
NCEP (augmented)†					
AUC = 0.78 (0.76–0.80)					
≥ 6	15	42 (38–46)	90 (89–92)	46 (42–50)	89 (88–90)
≥ 5	22	54 (50–59)	84 (83–85)	40 (37–43)	91 (89–92)
≥ 4	32	68 (65–72)	75 (74–77)	35 (32–37)	93 (91–93)
≥ 3	46	81 (78–84)	61 (60–63)	29 (27–31)	94 (93–95)

Data in parentheses are 95% CIs. %+, percentage of sample identified as screen positive by the detection rule. *NCEP metabolic syndrome rules: 1 point each for high waist circumference (women >88 cm or 35 in, men >102 cm or 40 in), raised blood pressure ($>130/85$ mmHg or using antihypertensive medication), low HDL cholesterol (<40 mg/dl for men and <50 mg/dl for women), high triglycerides (>150 mg/dl), and hyperglycemia (fasting glucose ≥ 6.1 mmol/l or ≥ 5.6 mmol/l). †Augmented metabolic syndrome score: 1 point for each element of the metabolic syndrome present (as above), except for fasting glucose (2 points when fasting glucose ≥ 5.6 mmol/l, or 5 points when fasting glucose ≥ 6.1 mmol/l); additionally, 1 point for obesity (BMI ≥ 30 kg/m²).

risk based on the metabolic syndrome definition rather than by entering numbers into a clinical calculator or webpage, the losses are small: lower sensitivity (2%) and specificity (4%) and a slightly greater percent of sample deemed positive (3%).

The properties we found for the NCEP definition (sensitivity of 50% and specificity of 82%) are similar to those found for IGT (52 and 92%, respectively) and for the same NCEP rule (53 and 85%, respectively) in a cohort of white and Mexican-American men and women (20). The sensitivity of the NCEP definition found in Finnish men was lower (41%) and specificity was higher (90%), perhaps because the NCEP waist cut point was too high in that setting (21). Lowering the cut point of impaired fasting glucose to 5.6 mmol/l, as recently recommended by the American Diabetes Association (16), produced an equally predictive, in terms of AUC, but more sensitive NCEP-based rule. Slight manipulations of the NCEP definition improved its predictive power and might serve as alternatives to those clinicians who prefer not to use risk functions.

A risk function built strictly on clinical variables, although having less overall predictability (AUC 0.71), was able to derive rules with sensitivities ranging from 40 to 77% and corresponding specificities ranging from 84 to 55%. A reported score composed of a slightly different set of

clinical variables also had good diagnostic properties (10), although, in that study, case definition was more stringent. Thus, rules based only on clinical information may be of value, for example, as a first step in serial diagnostic strategies for primary prevention in community settings.

Whether rules with $\sim 50\%$ sensitivity, such as IGT and those mentioned above, detect an adequate number of future cases of diabetes for prevention is debatable. The main point against rules with greater sensitivity is the consequent increase in resources necessary for interventions. However, to optimize resource use, one could categorize more than just high- and low-risk groups and implement graded intensities of interventions, according to the degree of risk. Our data suggest that cut points for such categorization of risk in middle-aged U.S. populations might be between deciles 5 and 6, and 8 and 9. As illustrated in Fig. 1, participants with estimated risk in the 9th and 10th deciles had, in fact, a risk of developing diabetes over 9 years of ~ 30 and 50%, respectively. In contrast, the risk of developing diabetes among individuals in the first five deciles ranged from $\sim 1\%$ to $\sim 9\%$.

The large community-based sample of white and African-American men and women followed over the current epidemic phase of diabetes in the U.S. and the use of split samples to generate and

validate rules presented strengthen the validity and generalizability of our findings. The nearly equivalent predictability of similar equations reported in other ethnic groups (8,9) suggests that these rules may also be applicable to other U.S. ethnic groups. In fact, the equation developed in non-Hispanic whites and Mexican Americans of the San Antonio Heart Study (8), when applied to our ARIC sample, produced an AUC (0.80) equal to that found when including a similar set of variables.

Yet, some limitations need to be considered. Losses to follow-up were not small. Although those lost presented a risk profile generally similar to those studied, their exclusion could possibly bias the diagnostic properties described. Because an OGTT was not done at baseline, some cases detected, especially early on, could be prevalent ones. Yet this, in fact, may increase the clinical relevance of our predictive equations, because undetected cases of diabetes not meeting the diagnostic criteria of fasting hyperglycemia are common in clinical practice. Additionally, our reported diagnostic properties would have been higher if only clinically diagnosed cases had been included. Finally, the sensitivities and specificities presented here for middle-aged adults, whites, and African Americans may not be applicable to younger or older groups or to those in other settings, re-

sulting in a different underlying risk of developing diabetes.

In conclusion, rules derived from readily available clinical information, alone or combined with simple laboratory measures, can characterize groups of middle-aged adults as having various degrees of diabetes risk. This categorization permits grading the intensity of preventive actions according to the degree of risk of each patient. Though further validation of these rules in other samples is important, they have immediate application. In addition to their use in clinical encounters, they can be applied by managed care organizations to existing databases to identify high-risk individuals. Algorithms based on these rules can also facilitate enrollment in clinical trials testing new strategies to prevent diabetes.

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References

- Venkat NK, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F: Diabetes: a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract* 50 (Suppl. 2):S77–S84, 2000
- 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
- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi 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
- 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
- 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
- Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002
- Stern MP, Williams K, Haffner SM: Do we need the oral glucose tolerance test to identify future cases of type 2 diabetes? *Diabetes Care* 26:940–941, 2003
- 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
- McNeely MJ, Boyko EJ, Leonetti DL, Kahn SE, Fujimoto WY: Comparison of a clinical model, the oral glucose tolerance test, and fasting glucose for prediction of type 2 diabetes risk in Japanese Americans. *Diabetes Care* 26:758–763, 2003
- Lindstrom J, Tuomilehto J: The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care* 26:725–731, 2003
- ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 129:687–702, 1989
- Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
- 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
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: 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
- Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
- Campbell G: Advances in statistical methodology for the evaluation of diagnostic and laboratory tests. *Stat Med* 13:499–508, 1994
- Efron B, Tibshirani RJ: *Introduction to the Bootstrap*. New York, Chapman and Hall, 1993
- Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM: Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 27:2676–2681, 2004
- Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM: The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 26:3153–3159, 2003
- Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA: Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 156:1070–1077, 2002