A Danish Diabetes Risk Score for Targeted Screening

The Inter99 study

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OBJECTIVE — To develop a simple self-administered questionnaire identifying individuals with undiagnosed diabetes with a sensitivity of 75% and minimizing the high-risk group needing subsequent testing.

RESEARCH DESIGN AND METHODS — A population-based sample (Inter99 study) of 6,784 individuals aged 30–60 years completed a questionnaire on diabetes-related symptoms and risk factors. The participants underwent an oral glucose tolerance test. The risk score was derived from the first half and validated on the second half of the study population. External validation was performed based on the Danish Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) pilot study. The risk score was developed by stepwise backward multiple logistic regression.

RESULTS — The final risk score included age, sex, BMI, known hypertension, physical activity at leisure time, and family history of diabetes, items independently and significantly ($P < 0.05$) associated with the presence of previously undiagnosed diabetes. The area under the receiver operating curve was 0.804 (95% CI 0.765–0.838) for the first half of the Inter99 population, 0.761 (0.720–0.803) for the second half of the Inter99 population, and 0.803 (0.721–0.876) for the ADDITION pilot study. The sensitivity, specificity, and percentage that needed subsequent testing were 76, 72, and 29%, respectively. The false-negative individuals in the risk score had a lower absolute risk of ischemic heart disease compared with the true-positive individuals (11.3 vs. 20.4%; $P < 0.0001$).

CONCLUSIONS — We developed a questionnaire to be used in a stepwise screening strategy for type 2 diabetes, decreasing the numbers of subsequent tests and thereby possibly minimizing the economical and personal costs of the screening strategy.

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Diabetes increases rapidly worldwide (1). In the U.S., the annual increase is currently 8.2%, probably due to the explosive increase in obesity over the last decade (2,3). In Denmark, the prevalence of diabetes by age 60 years has increased by 58% in men and by 21% in women over a period of 20 years, mainly due to increased BMI (4). In an ongoing Danish intervention study, the crude prevalence of diabetes was 6.3, and 65% of the individuals with diabetes were unaware of the disease (5), as was also found in previous studies (6,7). The age at onset of type 2 diabetes seems to decrease. In Denmark, type 2 diabetes is also diagnosed in young adults (5), and in the U.S., type 2 diabetes is frequently seen in young adults (8). Studies have shown that 30–50% of individuals with newly diagnosed type 2 diabetes have one or more microvascular or macrovascular complications at the time of diagnosis (6). Individuals with previously undiagnosed diabetes have an unfavorable cardiovascular risk profile compared with glucose-tolerant individuals, indicating a higher risk for cardiovascular disease (9–12). The American Diabetes Association (ADA) recommends regular screening for type 2 diabetes: patients should be screened at 3-year intervals beginning at age 45 years (13). In Denmark, regular screening is not recommended. Before implementation of screening, different uncertainties should be dissolved, including who should be screened, whether a high-risk group be identified, minimizing the need for subsequent testing, and whether screening is feasible.

The aim of the present study is to develop a simple risk score based on a self-administered questionnaire, which can identify at least 75% of individuals with diabetes and reduce the number of subsequent blood tests to 25%, and secondly, to evaluate the cardiovascular risk profile in individuals who are detected by the risk score compared with individuals who are missed (false negative) by the risk score.

RESEARCH DESIGN AND METHODS

— Based on a large population-based survey (Inter99) including 13,000 individuals (5), we subdivided the study population into two groups. The screening algorithm was developed based on the first half and validated in the sec-

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Abbreviations: ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; AUC, area under the curve; IGT, impaired glucose tolerance; IHD, ischemic heart disease; LADA, latent autoimmune diabetes in adulthood; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; SDM, screen-detected diabetes.

ond half of the study population. External validation was performed based on the Danish pilot of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study (14).

Inter99

Inter99 is a population-based primary prevention study of cardiovascular disease. An age- and sex-stratified random sample of 12,934 eligible individuals aged 30–60 years was invited. The participants were invited stratified on age and sex. They were born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, or 1969–1970. All participants born in the years ending with 4 or 9 were examined in 1999, whereas those ending with 0 or 5 were examined in 2000.

All participants completed a questionnaire containing information on symptoms of diabetes and risk factors for diabetes.

All participants without known diabetes underwent a 75-g standardized oral glucose tolerance test (OGTT). Plasma glucose, lipid, HbA_{1c}, C-peptide, and insulin levels were measured. Plasma glucose samples were immediately placed on ice and spun within 30 min. The glucose was analyzed using the hexokinase/G6P-DH (Boehringer Mannheim, Mannheim, Germany). HbA_{1c} was analyzed by ion-exchange high-performance liquid chromatography (BioRad, Richmond, CA). Serum cholesterol level was determined using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Serum C-peptide and serum insulin levels were measured at fasting and in relation to the OGTT. Serum C-peptide and serum insulin levels were analyzed using fluoroimmunoassay technique (AutoDelfia; Perkin Elmer-Wallac, Turku, Finland). Blood pressure was measured twice using a standard mercury sphygmomanometer with an appropriate size cuff after 5 min rest. Weight and height were measured with the participants wearing indoor clothes without shoes.

ADDITION pilot study

All people aged 40–69 years listed by five general practitioners in the city of Århus were invited to participate in the study. All participants completed a questionnaire containing the risk score. All participants underwent measurement of random capillary blood glucose. If the random blood glucose level was ≥4.5 mmol/l, a 75-g standardized OGTT was performed. The plasma glucose sample was placed on ice and spun within 60 min. The glucose was analyzed using the hexokinase/G6P-DH (Beckman, Fullerton, CA). Lipid and HbA_{1c} levels were analyzed with the same methods and in the same laboratory as in the Inter99 study. Blood pressure, height, and weight were examined in the same way in the two studies.

Definitions

Glucose tolerance was classified according to the World Health Organization (WHO) 1999 criteria (15). Individuals with normal glucose tolerance, impaired fasting glycemia, or impaired glucose tolerance (IGT) were considered nondiabetic. Individuals without known diabetes and fasting plasma glucose level ≥7.0 mmol/l or 2-h plasma glucose level ≥11.1 mmol/l were defined as having screen-detected diabetes (SDM). BMI was defined as weight in kilograms divided by height in meters squared (kg/m^2).

The 10-year absolute risk of having ischemic heart disease (IHD) was calculated by using the PRECARD program (16). Adjustment for age differences was done by calculating the 10-year absolute risk at a fixed age (60 years).

All participants gave written consent before taking part in the survey. The protocols were in accordance with the Helsinki declaration and approved by the local ethical committees.

Statistical analysis

Statistical analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC).

Development of the risk score

Symptoms and risk factors known clinically and from the literature to be associated with diabetes were selected to be evaluated. The selected symptoms were frequent thirst, frequent voluminous voiding of urine, weight loss, tiredness, and repeated cystitis. The selected risk factors included age, sex, family history of diabetes (either parents or siblings), known hypertension ("Have you ever been told that you have or have had hypertension?"), antihypertensive treatment, knowledge of dyslipidemia, treatment for hypercholesterolemia, and physical activity at leisure time in categories: sedentary, moderate, active, and competitive sport. Due to small numbers in the latter two groups, they were merged in the data analysis.

Univariate analyses were performed in two ways. First, the prevalence of diabetes in the selected variables was calculated, if this was substantially elevated among individuals positive for the selected variables, a logistic regression with SDM as the dependent variable was performed. Variables significant at 20% were included in the multiple logistic regression using stepwise backward elimination, with SDM as the dependent variable. The independent variables were categorized. A P value of 0.05 was considered significant. For each significant variable in the multiple logistic regression analysis, a score was calculated by multiplying the regression coefficients by 10 and rounding to the nearest integer. A sum score was calculated for each participant by adding the score for each variable in the risk model.

Validating the risk score

The predictive performance of the risk score was evaluated with respect to the area under the curve (AUC) in a receiver operating characteristics (ROC) curve, sensitivity (the probability of a positive test given the individual truly does have the disease), specificity (the probability of a negative test given the individual does not have the disease), the positive predictive value (the probability of the disease given a positive test), and the negative predictive value (the probability of being nondiseased given a negative test) in the three different populations. The CIs for the AUC, sensitivity, specificity, and predictive values were calculated using bootstrapping (1,000) (17). Furthermore, the proportion of individuals who needed subsequent testing (the proportion of individuals who have a score above the selected cutoff value in the risk score) was compared.

RESULTS

— In the Inter99 study, 6,784 (52.5%) of the invited individuals participated. Individuals with known diabetes (n = 139) or individuals who could not be classified according to the WHO classifications (n = 374) were excluded. Moreover, in 147 individuals, information on one or more of the other

Table 1—*Baseline characteristics of the three different cohorts: the first half of the Inter99 study, the second half of the Inter99 study, and the ADDITION pilot study*

	Inter99 first half	Inter99 second half	ADDITION pilot study
n	3,250	2,874	1,028
% IGT	12.6 (409)	10.9 (313)	9.2 (95)
% SDM	4.2 (135)	4.1 (117)	2.8 (29)
% Men	49.8 (48.1–51.5)	49.3 (47.5–51.2)	6.0 (42.9–49.1)
Age (years)	46.0 ± 7.9	46.0 ± 7.8	50.7 ± 7.8
BMI (kg/m^2)	26.2 ± 4.4	26.3 ± 4.6	25.1 ± 3.9
% BMI 25.0–29.9 kg/m^2	39.5 (37.8–41.2)	39.6 (37.8–41.4)	33.8 (30.9–36.8)
% BMI 30 kg/m^2	16.3 (15.1–17.7)	16.5 (15.2–17.9)	10.9 (9.1–13.0)
HbA_{1c} (%)	5.8 ± 0.5	5.8 ± 0.5	5.6 ± 0.5
% Known hypertension	18.6 (17.3–20.0)	17.6 (16.2–19.0)	19.3 (16.9–21.8)
Systolic blood pressure (mmHg)	129 ± 17	131 ± 17‡	142 ± 18§
Diastolic blood pressure (mmHg)	81 ± 11	84 ± 11‡	84 ± 11§
Total cholesterol (mmol/l)	5.5 ± 1.1	5.5 ± 1.1	5.8 ± 1.0§
% Parent having diabetes*	15.1 (13.9–16.3)	13.7 (12.5–15.0)	17.1 (14.8–19.5)
% Sibling having diabetes*	4.4 (3.7–5.2)	4.0 (3.3–4.8)	
% Physical inactive and moderate active	82.0 (80.7–83.3)	83.9 (82.5–85.2)	78.0 (75.4–80.5)†
% Daily smoker	36.8 (35.1–38.5)	34.5 (32.8–36.3)	31.0 (28.3–34.1)‡

Data are means ± SD or, where stated, percentages (95% CI). For % IGT and % SDM, values are percentages (*n*). Comparison of baseline characteristics between the population in which the algorithm was derived (first half of the Inter99 population) and the populations (the second half of the Inter99 population cohort and the ADDITION pilot study). *In the ADDITION pilot study only information on family history of diabetes (either parents or siblings) was available; †$P < 0.05$; ‡$P < 0.01$; §$P < 0.001$.

variables examined was missing, leaving 6,124 individuals for analysis.

Comparison between the three different populations

The risk score was derived from the first 3,250 participants, 135 (4.2%) of whom had SDM. The second half of the Inter99 population consisted of 2,874 individuals, 117 (4.1%) of whom had SDM. Finally, in the ADDITION pilot study, 1,028 (50%) accepted to participate and 29 (2.8%) had SDM. The baseline characteristics of the three different cohorts are shown in Table 1.

Development of the risk score

In Table 2, the first two columns show the univariate regression analysis for symptoms and risk factors for diabetes. After stepwise backward elimination of the nonsignificant variables, the final model included information on age, BMI, sex, known hypertension, physical activity, and family history of diabetes in parents (Table 2). Plausible interactions were tested between BMI and sex, BMI and knowledge of hypertension, sex and physical activity, sex and family history of diabetes, age and BMI, age and knowledge of hypertension, and age and physical activity, but none of these were significant (data not shown). Age was the strongest predictor for SDM followed by BMI and knowledge of hypertension. The score for each variable is shown in Table 2. Cutoff value of the sum score ≥31 showed a sensitivity close to the prespecified value but at a little higher proportion that needed subsequent blood tests (Table 3). Increasing the cutoff value decreased the sensitivity and the proportion that needed subsequent blood testing. Because a sensitivity ≥75% was prespecified, no more than 25% of the entire population might need subsequent testing; the cutoff value of ≥31 out of 60 points was chosen for evaluation.

Validation of the risk score

Internal validation. The performance of the risk score in the two validation populations is shown in the ROC curves (Fig. 1) and in Table 3. The AUC in the second half of the Inter99 was not significantly different from the AUC in the first half of the Inter99 (AUC 0.761 vs. 0.804; $P = 0.22$). The specificity, predictive values, and the percentage of the population that needed subsequent testing were similar in the two Inter99 populations, whereas the sensitivity tended to be lower in the second half of the Inter99 population compared with the first half of the Inter99 cohort, although not significantly (66.7 vs. 73.3%, $P = 0.25$). Individuals with diabetes in the second half of the Inter99 population were younger compared with the first half of the Inter99 cohort (mean age 49.5 vs. 51.5 years, $P = 0.03$) and had lower total cholesterol (5.8 vs. 6.1 mmol/l, $P = 0.02$), but there were no differences in blood pressure, BMI, and HbA_{1c}.

External validation. The AUC in the ADDITION pilot study was not significantly different from the AUC in the first half of the Inter99 population (AUC 0.804 vs. 0.803; $P = 0.99$). The sensitivity, specificity, predictive values, and proportion of individuals who needed subsequent testing by a cutoff ≥31 were alike in the first half of the Inter99 population and the ADDITION pilot study (Table 3).

Among individuals who screened positive, i.e., risk score ≥31, but who did not have SDM, 23.8 (95% CI 20.8–26.9), 20.6 (17.7–23.6), and 5.0% (2.8–8.3) had IGT in the first half of the Inter99 population, the second half of the Inter99 population, and the ADDITION pilot study, respectively.

In the first half of the Inter99 population, 409 had IGT, 190 of whom (sensitivity 46.5%; 95% CI 41.5–51.4%) were detected by the risk score with a cutoff ≥31. The corresponding sensitivities for the second half of the Inter99 population and the

Table 2—*Univariate and multivariate analyses of symptoms and risk factors for diabetes*

	Univariate regression		Multiple logistic regression			
Variable	Odds ratio	*P*	β-Coefficient	Odds ratio	95% CI	Risk score
Frequent thirst (yes vs. no)	1.00	0.99				
Frequent urination (yes vs. no)	0.6	0.17				
Tiredness (yes vs. no)	1.1	0.6				
Repeated cystitis (yes vs. no)	0.5	0.5				
Weight loss (yes vs. no)	0.7	0.6				
Hypertensive treatment (yes vs. no)	4.5	<0.0001				
Cholesterol measured (yes vs. no)	1.8	0.007				
Hypercholesterolemia (yes vs. no)	1.9	0.01				
Treatment for hypercholesterolemia (yes vs. no)	4.1	0.0044				
Smoking (yes vs. no)	1.0	0.86				
Sibling with diabetes (yes vs. no)	2.1	0.014				
Age						
45 vs. 30–40 years	1.8	0.11	0.6926	2.0	(1.0–4.1)	7
50 vs. 30–40 years	4.0	<0.0001	1.3111	3.7	(2.0–7.0)	13
55–60 vs. 30–40 years	7.0	<0.0001	1.8475	6.3	(3.5–11.5)	18
Sex (male vs. female)	1.5	0.02	0.3970	1.5	(1.0–2.2)	4
BMI						
25–29 vs. <25 kg/m^2	2.9	<0.0001	0.7401	2.1	(1.3–3.5)	7
30 vs. <25 kg/m^2	6.9	<0.0001	1.4672	4.4	(2.6–7.3)	15
Known hypertension (yes vs. no)	3.6	<0.0001	0.9832	2.7	(1.8–4.0)	10
Physical activity at leisure time (inactive versus active)	2.3	0.006	0.6488	1.9	(1.0–3.5)	6
Parent having diabetes (yes vs. no)	1.8	0.002	0.6835	2.0	(1.3–3.0)	7

The first two columns show the results in the univariate logistic regression analysis using SDM as the dependent variable. The final model is shown in the last four columns. A score for each variable in the model was calculated by multiplying the β-coefficients by 10.

ADDITION pilot study were 47.9 (42.3–53.6) and 45.2% (27.3–64.0), respectively.

Comparison of individuals with true-positive and false-negative risk scores

The cardiovascular risk profile was more unfavorable in the individuals who were true positive compared with those who were false negative: age (53.3 vs. 45.6 years, $P < 0.0001$), BMI (31.4 vs. 26.6 kg/m^2, $P < 0.0001$), systolic blood pressure (151 vs. 139 mmHg, $P < 0.001$), diastolic blood pressure (92 vs. 87 mmHg, $P < 0.001$), total cholesterol (6.0 vs. 5.7 mmol/l, NS), HDL cholesterol (1.2 vs. 1.4 mmol/l, $P < 0.0001$), and HbA_{1c} (6.8 vs. 6.3%, $P < 0.0001$). However, the percentage of daily smokers in the false-negative individuals was higher compared with the true-positive individuals (41.3 vs. 32.8%, NS). Using the above-mentioned risk factors, the absolute mean risk of having IHD within the next 10

Table 3—*Performance of the risk score in the three different cohorts*

	Sensitivity	Specificity	PV+	PV−	% Need subsequent testing
First half Inter99					
Cutoff					
29	79.3 (71.4–86.3)	68.7 (67.1–70.3)	9.9 (8.2–11.6)	98.7 (98.2–99.2)	33.3 (31.7–34.9)
30	77.0 (69.9–83.6)	70.2 (68.6–71.9)	10.1 (8.3–12.1)	98.6 (98.1–99.1)	31.8 (30.1–33.3)
31	73.3 (66.1–80.9)	74.3 (72.7–75.6)	11.0 (9.1–13.2)	98.5 (98.0–98.9)	27.7 (26.1–29.3)
32	68.9 (61.0–77.1)	78.0 (76.6–79.5)	12.0 (9.8–14.5)	98.3 (97.8–98.8)	23.9 (22.4–25.4)
Second half Inter99					
Cutoff 31	66.7 (58.1–74.5)	73.6 (71.9–75.2)	9.7 (7.5–11.7)	98.1 (97.5–98.7)	28.1 (26.4–29.7)
ADDITION pilot study					
Cutoff 31	75.9 (58.3–90.3)	72.2 (69.3–75.1)	7.3 (4.5–10.3)	99.0 (98.3–99.6)	29.2 (26.1–32.0)

Data are percentages and 95% CI calculated by bootstrapping (1,000). PV+, positive predictive value; PV−, negative predictive value.

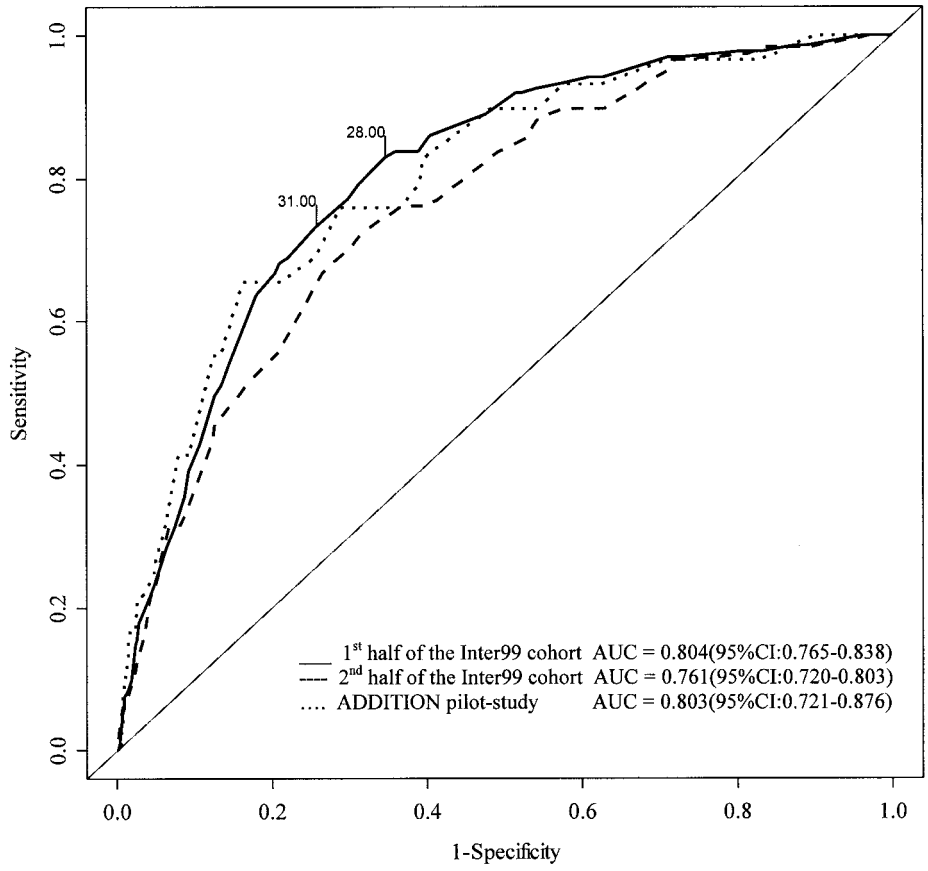

Figure 1—*ROC curves for the risk score in the three different cohorts. The two cuts on the development cohort curve indicate a sum score of 31 and 28, respectively.*

years was 20.4% in the true-positive individuals compared with 11.3% in the false-negative individuals ($P < 0.0001$). The differences persisted after adjustment for age and absolute mean risk for IHD at age 60 years (25.2 vs. 20.6% in true-positive and false-negative individuals, respectively; $P < 0.0001$). In the false-negative individuals, the mean fasting C-peptide was 795.6 pmol/l compared with 1,049.9 pmol/l ($P < 0.001$) in the true-positive individuals, whereas there was no difference in 2-h C-peptide. Similar trends were seen for serum insulin.

CONCLUSIONS — In this study, we developed a simple pragmatic risk score based on a one-page questionnaire. This risk score identifies 75.9% of individuals with previously undiagnosed type 2 diabetes. Furthermore, the risk score has a specificity of 72% and decreases the proportion of individuals in the population that need subsequent testing to 29%. Several other risk scores have been developed, primarily in Caucasians (18–21). The performances of these risk scores are similar to the Danish risk score, although there are minor differences in specificity and the number of individuals needing subsequent testing. The questionnaire derived on National Health and Nutrition Examination Survey (NHANES) data (19) had a lower specificity (65%), the risk scores developed in Holland had also a lower specificity (55 and 56%), and 45% of the entire population needed subsequent testing in the risk score developed by Ruige et al. (20). The advantages of the Danish risk score are, first, that it is developed in a population including the young age-groups in which the proportion of individuals with undiagnosed diabetes constitutes up to 80% of all individuals with diabetes (5). Second, this questionnaire can be completed without any specific measurements, and therefore, the questionnaire can be answered at home, in contrast to the Cambridge risk score (21), which is based on measurements and information known by the general practitioner and thus dependent on electronic registration of risk factors for type 2 diabetes in general practice.

Instead of dividing the Inter99 population into two equally sized samples by random, we divided the Inter99 population into two parts based on the invitation date because the risk score should be used in the ADDITION study before finishing the baseline examination of the entire Inter99 population. Because the Inter99 population was invited stratified on age and sex, this approach was acceptable.

The sensitivity and the percentage of the entire population that should undergo further testing were predefined. The rationale behind these was, first, that the health care system (general practitioners) could only manage to test 25% of the entire adult population and, second, that because a risk score is the first step in a stepwise procedure, the sensitivity must not be <75%. These predefinitions were used to identify the cutoff defining an individual as being at high risk. In contrast, many previous studies have used ROC curves, and it has been recommended that ROC curves should be used to find the optimal threshold in screening and diagnostic tests (22). The ROC curves are superior in visualizing the differences in the accuracy of a test in different populations or to visualize the accuracy in differ-

ent tests in the same population, and this is quantified as a single number through the AUC. Mathematically, the optimal threshold in ROC curves is defined as the 45 tangent in the upper left corner of the plot, i.e., the point maximizing the sum of sensitivity and specificity (23). Clinically, however, this may not be the optimal cutoff for a test because sensitivity versus specificity must be weighted against the seriousness of the disease, the test under evaluation (whether it is a questionnaire or an invasive test), whether the test is a part of a screening strategy or a single screening test, and how often the test should be offered, etc.

A risk score based on questions regarding phenotypical characteristics for type 2 diabetes could never obtain a sensitivity of 100%, because some individuals with type 2 diabetes are lean and some individuals will have latent autoimmune diabetes in adulthood (LADA) and, therefore, have a phenotype more like individuals with type 1 diabetes (24). The prevalence of LADA in the population is unknown: some studies have shown that ~10% of individuals with known type 2 diabetes do have GAD antibodies (24). We found that the false-negative individuals in the risk score had lower fasting C-peptide and fasting insulin levels; however, there was no difference in postchallenge C-peptide and insulin compared with the true-positive individuals. In addition, the individuals in the false-negative group were leaner and younger, indicating that some of these individuals may have had LADA.

In our risk score, 24% of individuals with previously undiagnosed diabetes will be missed. We have shown that these individuals do have a more favorable cardiovascular risk profile and, therefore, a lower absolute risk of IHD compared with the individuals detected by the risk score. The difference between absolute risks of 25.2% in the true-positive group compared with 20.6% in the false-negative group is due to the difference in risk profile. The implication of all of the risk factors except smoking is even higher because of the high smoking prevalence among the false-negative individuals. This is in accordance with previous findings by Spijkerman et al. (25), who in a 10-year follow-up study found that true-positive cases had a relative risk of age- and sex-adjusted all-cause mortality of 1.73 (1.08–2.78) compared with the nondiabetic individuals (true-negative individuals), whereas false-negative individuals had a relative risk of 1.52 (0.55–4.16) (25). Because screening is an ongoing process, presumably, some of the false-negative individuals will become true positive over time and will be picked up in a subsequent screening.

Several risk scores have been developed in Caucasians, and the question is whether better risk scores can be developed without losing simplicity and thereby decreasing compliance. The existing risk scores are comparable with respect to performance, indicating that little can be gained from further modifications. It is, however, relevant to evaluate generalizability across countries and ethnic groups.

In conclusion, we have developed a simple one-page questionnaire that can be used in a stepwise screening strategy for type 2 diabetes in Denmark.

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