Diabetic Patients Detected by Population-Based Stepwise Screening Already Have a Diabetic Cardiovascular Risk Profile

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OBJECTIVE — To describe a population-based two-step screening procedure for type 2 diabetes and to study the cardiovascular risk profile of the patients identified by the screening.

RESEARCH DESIGN AND METHODS — The first step of the screening procedure consisted of the Symptom Risk Questionnaire (SRQ), and the second step was a fasting capillary glucose measurement. In subjects with an SRQ score of >6 and a capillary glucose level of >5.5 mmol/l, an oral glucose tolerance test was performed.

RESULTS — A total of 11,679 inhabitants of the West-Friesland region of the Netherlands, aged 50–75 years, were invited. Of the inhabitants, 9,169 (78%) responded, and, of those, 417 had previously diagnosed diabetes. The SRQ score was calculated for 7,736 participants, and 3,301 of those had a score of >6. A total of 2,885 subjects (87.3%) attended for capillary glucose measurement. Diagnostic testing was carried out in 509 participants, and we identified 217 diabetic patients. In these patients detected by screening, mean HbA_{1c} was 6.7% (±1.4). Hypertension and high total cholesterol levels (>5.0 mmol/l) were present in 70%, 33% had high triglyceride (>3.0 mmol/l) or low HDL cholesterol levels (<1.0 mmol/l in men and <1.1 mmol/l in women), and 40% were obese (BMI ≥30 kg/m^2).

CONCLUSIONS — The high response rate was the main feature of the screening by means of the Symptom Risk Questionnaire and fasting capillary glucose measurement followed by diagnostic testing. The 217 diabetic patients detected by the screening were characterized by relatively low HbA_{1c} levels and by a cardiovascular risk profile typical of diabetic patients.

Diabetes Care 25:1784–1789, 2002

Screening for type 2 diabetes has been promoted in the American Diabetes Association guidelines and the medical literature (1,2). The high prevalence of undiagnosed diabetes (3,4), the presence of diabetic complications at the time of diagnosis (5), and the assumption that early detection and treatment will be beneficial have lead to these recommendations.

Screening for type 2 diabetes can be carried out in various ways. Population-based or universal screening attempts to screen every person in the entire population or in an entire age-group. Selective or targeted screening is directed at individuals with a high prevalence of risk factors. Opportunistic screening consists of screening people during their visits to, for example, the general practitioner's office (6). Universal screening for type 2 diabetes with oral glucose tolerance tests (OGTTs) performed in the whole population is burdensome because it is invasive and time consuming. Targeted screening with a noninvasive test for first selection, followed by glucose testing in high-risk individuals only, might be a more efficient approach.

Studies on universal screening (7,8), opportunistic screening in general practice (9), and targeted screening in general practice (10) have been reported, but few data exist on population-based targeted screening for type 2 diabetes.

In this article, we report on a population-based two-step screening procedure and the cardiovascular risk profile of individuals identified as diabetic patients. The two-step screening consisted of a screening questionnaire (step 1) (Symptom Risk Questionnaire [SRQ] [11]) and a fasting capillary glucose sample (step 2) followed by an OGTT.

RESEARCH DESIGN AND METHODS

Study population

From 1998 to 2000, all inhabitants aged 50–75 years (n = 11,679) and living in three municipalities in the semi-rural region of West-Friesland, the Netherlands, were invited to participate in the screening for type 2 diabetes.

Screening procedure

All individuals received an invitation with a cover letter explaining the aim of the study, an informed consent form, the SRQ, a nonparticipation form, and an en-

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Received for publication 7 January 2002 and accepted in revised form 29 June 2002.

Abbreviations: OGTT, oral glucose tolerance test; SDM, screening-detected type 2 diabetes; SRQ, Symptom Risk Questionnaire; WHO, World Health Organization.

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

velope with prepaid postage. After 6 weeks, a reminder was sent to all people who did not respond to the first invitation. The first step of the screening consisted of the completion of the SRQ, which contains nine questions about age, sex, BMI, family history of diabetes, frequent thirst, use of antihypertensive medication, shortness of breath, claudication, and cycling. Each answer has a fixed score, and the aggregate SRQ score is a predictor of undiagnosed type 2 diabetes (11). The cut point of six had optimal sensitivity (66%) and specificity (70%) (positive predictive value 13%, negative predictive value 97%) for diabetes, as defined by the 1999 World Health Organization (WHO) diagnostic criteria (A.M.W.S., J.M.D., unpublished data). All participants with an SRQ score of >6 points were invited for the second step of the screening, which consisted of a fasting capillary blood glucose measurement. Capillary glucose was measured in whole blood samples with a Hemocue Blood Glucose Analyzer, a portable photometric system based on the glucose-dehydrogenase method (Hemocue Benelux, Oisterwijk, the Netherlands). Intra- and interassay coefficients of variation ranged from 1.0 to 4.5% and from 2.4 to 4.2%, respectively (12,13). In all individuals with a capillary glucose level >5.5 mmol/l, which is the threshold for glucose intolerance in the guidelines of the Dutch College of General Practitioners (14), a venous sample was drawn at the same occasion. Participants with a capillary glucose level >5.5 and ≤8.5 mmol/l had a 75-g OGTT within 2 weeks. Individuals with a capillary glucose level >8.5 mmol/l did not have an OGTT because their fasting levels were considered to be too high. Therefore, only a second fasting plasma glucose measurement was determined, and diagnosis was based on two fasting plasma glucose measurements. For all participants, 1999 WHO diagnostic criteria were used: a fasting plasma glucose level ≥7.0 mmol/l on two separate occasions or a 2-h plasma glucose level ≥11.1 mmol/l (15). Individuals identified as having screening-detected type 2 diabetes (SDM) were invited for an extensive medical examination including measurement of HbA_{1c}, glucose, blood lipids, anthropometry, and blood pressure. The study was done at the Diabetes Research Center in Hoorn, the Netherlands. All participants gave written informed consent. The Ethics Committee of the VU University Medical Center approved the study.

Measurements

Plasma glucose concentrations were assessed by means of a glucose hexokinase method (Boehringer Mannheim, Mannheim, Germany). HbA_{1c} was determined by ion-exchange high-performance liquid chromatography with a Modular Diabetes Monitoring System (Bio-Rad, Veenendaal, the Netherlands). Serum total cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic techniques (Boehringer Mannheim). The Friedewald formula was used to calculate LDL cholesterol, except when the triglyceride level was >4.5 mmol/l. Weight and height were measured with subjects barefoot, wearing only light clothes. Blood pressure was calculated as the mean of two measurements, performed in the sitting position after 5 min of rest, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, U.K.).

High cholesterol was present if serum total cholesterol was >5.0 mmol/l. Low HDL cholesterol was defined as HDL cholesterol <1.0 mmol/l in men and HDL cholesterol <1.1 in women and high LDL cholesterol as LDL cholesterol ≥3.0 mmol/l. High triglyceride was defined by a triglyceride level >2.0 mmol/l (16). A ratio of total cholesterol to HDL cholesterol of >5 was considered to be high (14). Obesity was defined as BMI ≥30 kg/m^2 (17). Individuals were considered to be hypertensive if they had a diastolic blood pressure ≥90 mmHg and/or a systolic blood pressure ≥140 mmHg, and/or if they were using antihypertensive medication (18).

To study whether subgroups with different cardiovascular risk profiles could be distinguished, we compared three subgroups. First, the patients with fasting capillary glucose >8.5 mmol/l who did not have an OGTT (non–OGTT-SDM) were compared with patients who did (OGTT-SDM). Next, within the group of OGTT-SDM patients, we compared two groups: the 2-h SDM group consisted of patients for whom the 2-h value of the OGTT was decisive for diagnosis because they had none or only one elevated fasting value. The mixed SDM group included patients who had an OGTT and who had two elevated fasting values. Some of these patients also had an elevated 2-h value.

Statistical analysis

Groups were compared using the Student's *t* test for continuous variables, the χ^2 test for dichotomous variables, and the Mann-Whitney *U* test for skewed variables. A *P* value of <0.05 was considered statistically significant. Triglycerides and the SRQ score were presented as median and interquartile range because of their skewed distribution.

RESULTS

Two-step screening procedure

Response. Figure 1 shows the outline of the stepwise screening procedure and the number of participants in each step. A total of 11,679 individuals were invited. Of those, 2,510 (22%) subjects did not respond at all. There were 9,169 people who sent back either the SRQ or the nonparticipation form, resulting in a total response of 78%. The 741 people who returned the nonparticipation form were significantly older than the participants of the screening. Nonparticipants reported various reasons: 28.5% checked the item "I am certain that I do not have diabetes," 15.7% checked "My health is already monitored by a physician," and 13.8% checked "a recent blood glucose test was OK." In total, 417 previously diagnosed diabetic patients completed the SRQ. The SRQ was returned by a total of 8,011 nondiabetic participants, but because of missing data ($n = 275$), we calculated the SRQ score for 7,736 participants. Of 3,301 individuals with an SRQ score of >6 points, 2,885 participated in the fasting capillary glucose measurement, and 570 had a glucose level >5.5 mmol/l. Of these, 38 had a capillary glucose level >8.5 mmol/l, and no OGTT was performed, but two venous fasting samples were taken. An OGTT was carried out in 473 individuals. A total of 217 participants were identified by the screening procedure as having type 2 diabetes. A physical examination was performed in 195 patients.

Nonresponse. Table 1 shows the nonresponse in various stages of the screening procedure and diagnostic testing. The nonresponse rate varied from 21% in the very first step of the screening to 11% in the diagnostic test. We found that the nonresponders of the first screening step (completion of the SRQ) were more likely

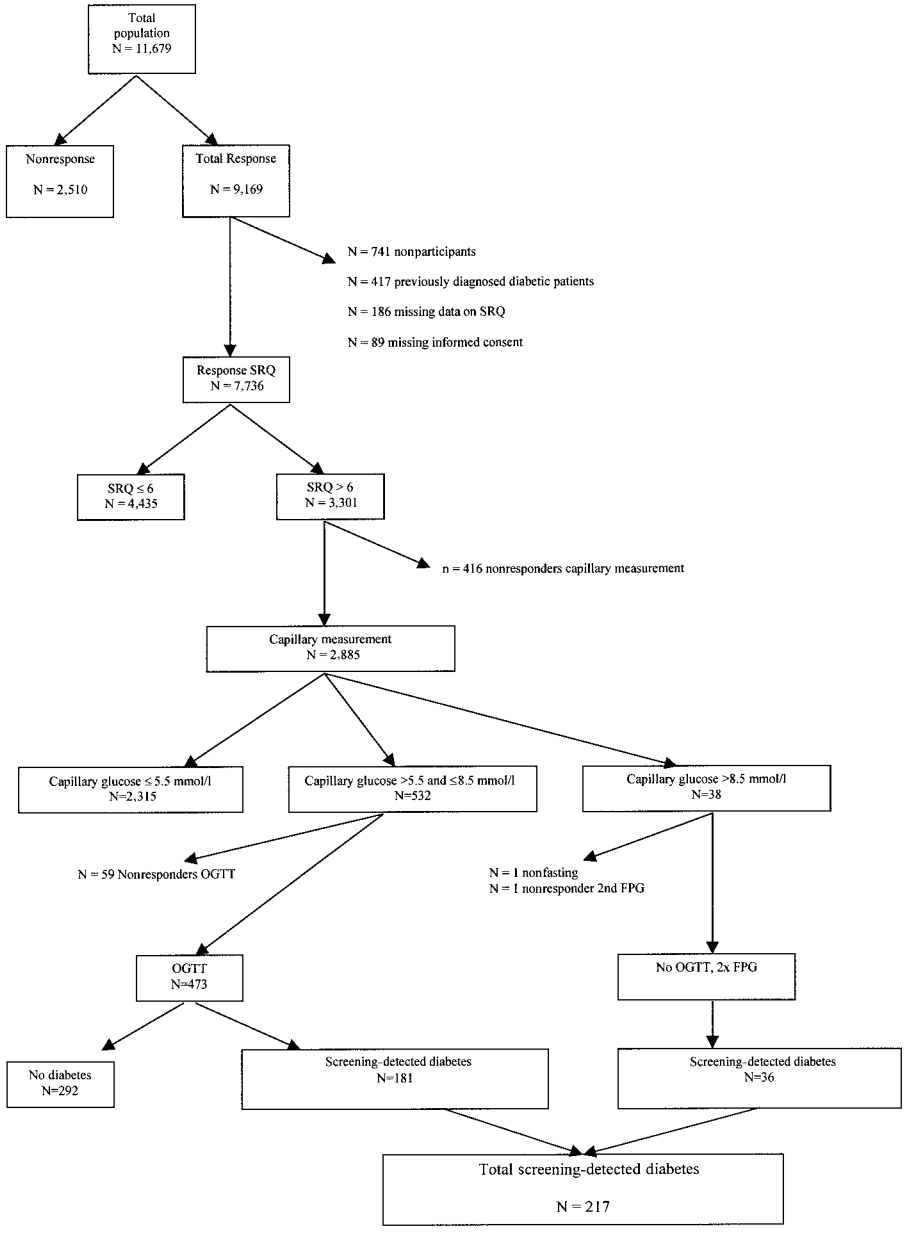

Figure 1—*Outline of the stepwise population-based screening study. FPG, fasting plasma glucose.*

to be men and to be younger than the participants. The nonresponders for the OGTT were older than participants.

Screening and diagnostic tests

Table 2 shows results of screening and diagnostic tests of all SDM patients and subgroups. The non–OGTT-SDM group was younger than the OGTT-SDM group, although not significantly so. The statistically significant differences in capillary and fasting glucose levels between the groups were a consequence of the subgroup definition.

Clinical characteristics

Table 3 shows clinical characteristics of all SDM patients and subgroups. Diabetic dyslipidemia (high triglycerides and low HDL cholesterol levels) was present in approximately one-third of all diabetic patients. High cholesterol and hypertension were each present in ~70% of diabetic patients. The non–OGTT-SDM and OGTT-SDM groups were comparable for lipid levels, anthropometric measures, and blood pressure. HbA_{1c} levels were significantly higher in the non–OGTT-SDM group, but low HDL cholesterol in men was significantly less frequent when compared with the OGTT-SDM group. Blood pressure in the 2-h SDM group was significantly higher than that in the mixed SDM group, but lipid levels were significantly more favorable in 2-h SDM patients (low triglycerides and, in women, no low HDL cholesterol). Fourteen individuals in the 2-h SDM group had isolated postchallenge hyperglycemia. Compared with the other SDM patients, they had significantly lower glucose and HbA_{1c} levels and were significantly less obese.

CONCLUSIONS — Screening is directed at the identification of patients in the early stages of the disease. In the present study, this was reflected by the relatively low HbA_{1c} levels in SDM patients. The prevalence of hypertension and high total cholesterol was similar to prevalence rates found in 15 patients in a universal screening study (7) but was higher compared with prevalence rates from an opportunistic screening study (9). In the latter study, however, the definitions of hypertension and high lipid levels were not standardized for the whole study population but varied between general practices. In a study of diabetic patients recently diagnosed by their general practitioner, the prevalence of hypertension was 61%, and abnormal lipids were present in 78% of patients (19). In summary, prevalence of hypertension and dyslipidemia in our study was of the same magnitude or even slightly higher than that reported in other screening studies and in newly detected diabetic patients.

The prevalence rates of dyslipidemia, obesity, and hypertension in our study may be high because the SRQ includes BMI and several cardiovascular items, thus selecting a group of individuals with an unfavorable cardiovascular risk profile. One could argue that our screening procedure identified diabetic patients who might benefit most from early treatment of dyslipidemia and hypertension. The Heart Protection Study and the Cholesterol and Recurrent Events trial have already shown that type 2 diabetic patients do benefit from treatment of dyslipidemia in terms of reduction of lipid levels (20,21) and reduction in the number of major coronary events (21). Treatment of hypertension in type 2 diabetic patients has been demonstrated to reduce cardiovascular events and deaths related to diabetes (22).

Table 1—*Nonresponse in various stages of the screening procedure and diagnostic testing*

Screening step/diagnostic test	Responders	Nonresponders
Total population		
n	11,679	—
Age (years)	59.6 ± 7.1	—
Sex (% male)	50.9	—
SRQ		
n (%)	7,736 (66)	2,510 (21)
Age (years)	59.4 ± 6.9	58.8 ± 7.0*
Sex (% male)	49.0	56.4*
Capillary measurement		
n (%)	2,885 (87.3)	416 (12.6)
Age (years)	63.2 ± 6.7	63.0 ± 7.1
Sex (% male)	48.6	46.4
OGTT		
n (%)	473 (88.9)	59 (11.1)
Age (years)	63.1 ± 7.1	65.1 ± 6.3
Sex (% male)	49.9	50.8
SRQ score	11 (9–14)	11 (9–14)
Capillary glucose (mmol/l)	6.1 ± 0.6	6.1 ± 0.5

Data are means ± SD or median (interquartile range) unless otherwise indicated. *Nonresponders significantly different from responders.

The subgroup of non–OGTT-SDM patients seemed to be patients in whom diabetes was already in a more advanced stage because they were relatively young, had high HbA_{1c} levels, and frequently reported thirst and a family history of diabetes on the SRQ (SRQ data not shown). Nevertheless, their cardiovascular risk profile did not differ from that of patients diagnosed by the OGTT. Because of the symptoms and high fasting glucose values, we expect that these patients would also have come to (rapid) clinical recognition without the screening.

The 2-h SDM group would not have been diagnosed if the OGTT had not been performed. Apart from the higher prevalence of hypertension, this group did not differ from the remaining SDM patients. Moreover, in the Netherlands, >50% of these patients would probably have been tested again within 1 year because they had one fasting plasma value in the diabetic range in addition to the elevated 2-h value (14). The small group with isolated postchallenge hyperglycemia and with lower levels of fasting glucose, HbA_{1c}, and BMI would not have been identified at all without the OGTT. In other words, without the OGTT, we would have missed only a small group of patients with a similar cardiovascular risk profile. These results seem to imply that the OGTT added relatively few cases and may not be required to identify the large majority of diabetic patients in this two-step screening procedure.

The application of screening and diagnostic tests inevitably involves some misclassification. We probably have missed some individuals who did have diabetes but did not have the risk factors included in the SRQ, i.e., the young, less obese diabetic patients without a family history of diabetes and without cardiovascular symptoms. Because of the younger age and absence of cardiovascular symptoms, one could speculate that this group of missed patients would have a more favorable cardiovascular risk profile. The total population prevalence of undiagnosed diabetes and the number of missed diabetic patients can only be determined by population screening. However, this was not feasible. The difference between the prevalence of screening-detected diabetes in a screening study and the prevalence of undiagnosed diabetes from a population study might seem a good approximation of the number of missed patients. However, major differences between populations in true diabetes prevalence, quality of health care, and routine detection of type 2 diabetes and participation rates prohibit the comparison of results of different studies. The same is true for the comparison of prevalence rates of screening-detected diabetes among screening studies.

Engelgau et al. (6) stated in his review of screening for type 2 diabetes that glucose (invasive) tests performed better than the screening questionnaires. Still,

Table 2—*Screening and diagnostic test results of screening-detected diabetic patients*

			OGTT-SDM	
	All SDM	Non–OGTT-SDM	2-h SDM	Mixed SDM
n	217	36	36	145
Age (years)	63.6 ± 7.0	62.6 ± 7.8	64.3 ± 6.5	63.6 ± 6.9
Sex (% male)	51.6	50.0	52.8	51.7
SRQ score	12 (9–16)	11 (9.25–15)	12 (9.3–14.8)	12 (9–17)
Fasting capillary glucose (mmol/l)	7.4 ± 2.2	11.4 ± 2.6*	5.9 ± 0.3†	6.7 ± 0.7
First FPG (mmol/l)	8.6 ± 2.5	13.1 ± 2.9*	6.8 ± 0.4†	7.9 ± 0.8
Second FPG (mmol/l)	7.8 ± 0.9	12.9 ± 2.7*	6.9 ± 0.5†	8.1 ± 0.9
2-h plasma glucose (mmol/l)	12.3 ± 3.7	—	12.8 ± 1.4	12.2 ± 4.1

Data are means ± SD or median (interquartile range) unless otherwise indicated. 2-h SDM, 2-h value of the OGTT decisive for diagnosis, with none or only one elevated fasting value; FPG, fasting plasma glucose; mixed SDM group, two elevated fasting values or two elevated fasting and elevated 2-h values; non–OGTT-SDM, patients with fasting capillary glucose >8.5 mmol/l, diagnosed on two fasting values, with no OGTT performed; OGTT-SDM, patients diagnosed on OGTT. *Non–OGTT-SDM significantly different from OGTT-SDM; †2-h SDM significantly different from mixed SDM.

Table 3—*Clinical characteristics of screening-detected diabetic patients*

	All SDM	Non–OGTT-SDM	OGTT-SDM	
			2-h SDM	Mixed OGTT-SDM
n	195	33	29	133
HbA_{1c} (%)	6.7 ± 1.4	8.8 ± 1.5*	5.8 ± 0.5†	6.4 ± 0.9
Cholesterol (mmol/l)	5.7 ± 1.1	5.7 ± 1.2	5.5 ± 1.0	5.8 ± 1.1
High cholesterol (%)	73.1	66.7	69.0	75.6
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.2 ± 0.3	1.3 ± 0.4	1.3 ± 0.4
Low HDL				
Women (%)	27.7	43.8	0†	28.8
Men (%)	35.4	11.8*	16.7	41.5
Cholesterol/HDL ratio	4.84 ± 1.45	5.00 ± 1.77	4.46 ± 1.29	4.88 ± 1.39
High cholesterol/HDL ratio (%)	35.9	36.4	27.6	44.3
LDL cholesterol (mmol/l)	3.57 ± 0.96	3.59 ± 0.96	3.46 ± 0.81	3.59 ± 0.99
High LDL (%)	77.2	74.2	71.4	79.2
Triglycerides (mmol/l)	1.7 (1.2–2.4)	1.6 (1.2–2.4)	1.4 (1.0–1.9)†	1.8 (1.3–2.4)
High triglycerides (%)	34.2	33.3	17.2†	38.2
Lipid-lowering therapy (%)	20.4	13.9	25.0	20.8
BMI (kg/m^2)	29.8 ± 5.3	29.9 ± 6.4	28.4 ± 4.1	30.1 ± 5.3
Obesity (%)	40.0	36.4	31.0	42.9
Systolic blood pressure (mmHg)	141 ± 18	141 ± 19	148 ± 15†	140 ± 19
Diastolic blood pressure (mmHg)	86 ± 10	88 ± 11	88 ± 8	85 ± 9
Antihypertensive medication (%)	45.2	38.9	44.4	47.2
Hypertension (%)	69.6	69.4	75.0	68.3

Data are means ± SD for continuous variables and median (interquartile range) for triglycerides. High total cholesterol: cholesterol >5.0 mmol/l; low HDL cholesterol: HDL cholesterol <1.0 mmol/l for men and HDL cholesterol <1.1 for women; high LDL cholesterol: LDL cholesterol ≥3.0 mmol/l; high triglycerides: triglycerides >2.0 mmol/l; high cholesterol/HDL cholesterol ratio >5. Obesity: BMI ≥30 kg/m^2. Hypertension: diastolic blood pressure ≥90 mmHg, systolic blood pressure ≥140 mmHg, and/or use of antihypertensive medication. 2-h SDM group, 2-h value of the OGTT decisive for diagnosis, with none or only one elevated fasting value; mixed SDM group, two elevated fasting values or two elevated fasting and elevated 2-h values; non–OGTT SDM, patients with fasting capillary glucose >8.5 mmol/l, diagnosed on two fasting values, with no OGTT performed; OGTT-SDM, patients diagnosed on OGTT. *High fasting SDM significantly different from OGTT-SDM; †2-h SDM significantly different from mixed SDM.

we feel that in the selection of a screening test, other aspects of screening should prevail, for example, *1*) the fact that screening tends to involve a high number of people relative to the number who benefit eventually (23) and *2*) that there is still no convincing evidence for the benefits of early diagnosis and treatment of type 2 diabetes (6,24).

In this context, we believe that a noninvasive screening test should be the test of choice. Naturally, this noninvasive screening test should have good test characteristics. We selected the SRQ, which was developed in a Dutch population and had the best performance of three questionnaires (11).

Organization of the screening procedure is likely to influence participation rates. Nonresponse rates in other screening studies ranged from 65% in the screening test (7) to ~25% in diagnostic testing (7,9). In our study, the nonresponse was 22% in the first screening test (SRQ) and 11% for the diagnostic test (OGTT). Lawrence et al. (7) used a fasting plasma glucose test as the first screening tool. In contrast, in the present study, only people with a higher risk of undiagnosed diabetes (high SRQ score) were asked to go through the trouble of fasting for a capillary glucose measurement. The need to fast again for a diagnostic test was also restricted to those with a high capillary glucose level. We would like to stress that high-risk individuals with a negative OGTT result should be informed that they do not have diabetes at this very moment but that they still have an elevated future risk. In conclusion, our targeted screening procedure is less of a burden for its participants than universal screening because the first screening test is noninvasive, and further invasive diagnostic testing is restricted to people at high risk for undiagnosed diabetes. Targeted screening might result in a cost advantage as well because of the smaller number of diagnostic tests, which will save money in terms of time, personnel, and laboratory costs.

Recently, O'Connor et al. (25) described a stepwise screening within a health management organization. The first selection of the high-risk population was based on information available in databases. Consequently, there was no initial loss due to nonresponse. However, the participation rates for the subsequent glucose tests were lower than in our population-based targeted screening, and only a few patients were identified. The quality of diabetes care within this health management organization might have affected the yield of screening, as was shown by the high proportion of people who were screened for diabetes in the previous year. The differences between these two screening studies illustrate that comparisons of screening studies need to be interpreted with caution.

The results of our study showed that it was possible to carry out population-based stepwise screening. We succeeded in identifying 217 patients with type 2 diabetes, but we cannot say whether these patients will benefit from their early identification in terms of health status or

whether the screening is cost-effective. Future screening studies should focus on the quantification of possible benefits of early detection followed by early treatment.

In conclusion, our results show that stepwise population screening by means of the SRQ and a fasting capillary glucose measurement followed by diagnostic testing was an acceptable and practical method of screening for type 2 diabetes. The diabetic patients detected by the screening were characterized by relatively low HbA_{1c} levels and a cardiovascular risk profile typical of diabetic patients.

Acknowledgments— This study was funded by the Health Research and Development Council of the Netherlands (formerly the Prevention Fund).

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