

ORIGINAL PAPER

What is the risk of mortality for people who are screen positive in a diabetes screening programme but who do not have diabetes on biochemical testing? Diabetes screening programmes from a public health perspective

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Objectives: To assess mortality risk in people classified by the Cambridge risk score (CRS), a previously validated simple screening tool for undiagnosed type 2 diabetes that uses only information routinely available in primary care.

Setting: Random sample of the general population between 50 and 75 years of age in Hoorn, The Netherlands

Methods: The results of the CRS were compared with the gold standard for diabetes, the oral glucose tolerance test (OGTT) results classified according to the World Health Organisation (WHO) 1999 diagnostic criteria. Cox's proportional hazards regression was used to assess the risk of mortality of screen positive and screen negative people.

Results: 154 people out of the total population of 2297 had previously undiagnosed diabetes and 113 (73%) of these would have been detected with the CRS (true positive). However, the CRS identified a much larger group (n=1037) who were positive for the score, but who did not have diabetes on biochemical testing (false positive). Unadjusted risk of mortality was highest in the true positive group (3.40 95% confidence interval (95% CI, 2.15 to 5.38)), intermediate in false positive people (2.62 (2.00 to 3.43)), and lowest in false negative people (1.50 (0.55 to 4.09)) with the true negative group as reference. Adjustment for age and sex resulted in similar risk estimates for all three groups, but mortality risk was significantly increased only in false positive and true positive groups compared with the true negative group.

Conclusions: People who have a positive risk score are at high risk of mortality whether or not subsequent testing shows them to have diabetes. Direct public health interventions in this high risk population may be appropriate.

The purpose of screening for type 2 diabetes is to differentiate an asymptomatic person at high risk from a person at low risk for type 2 diabetes.¹ Those at high risk can then be offered diagnostic testing and subsequent treatment aimed at minimising the complications of diabetes, in particular cardiovascular disease. There is continuing uncertainty about the overall benefits and harms of screening for type 2 diabetes.^{2,3} In the absence of evidence supporting universal screening, targeted screening has been proposed as an alternative. One possible approach is to screen with a risk score^{4,5} or risk questionnaires^{6,7} with subsequent diagnostic biochemical testing restricted only to those people who have a score that exceeds a predefined threshold.

Griffin *et al* previously developed and evaluated the Cambridge Risk Score (CRS), an instrument that uses routinely available data from general practice records to identify people at high risk of having undiagnosed type 2 diabetes.⁴ The CRS was effective at identifying people with previously undiagnosed diabetes and more efficient than universal population screening because only those at risk were invited for glucose testing.⁴

In targeted screening programmes for type 2 diabetes, the focus is on the population who screen positive and in whom the diagnosis is confirmed by biochemical testing. Little is known about the risk of mortality in people who are screen positive but who do not have diabetes. This paper describes the mortality risk in people with a positive screening test for type 2 diabetes with data from the Hoorn study, a prospective population based cohort study of glucose intolerance and cardiovascular disease.

METHODS

Population

The Hoorn study is a prospective population based study of glucose intolerance and has been described previously.⁸ Briefly, 3553 white men and women were randomly selected from the population register of the City of Hoorn and 2484 people agreed to participate. Follow up of information on vital status was complete until 1 January 2000. The ninth revision of the international classification of diseases (ICD-9) was used to code the causes of death.⁹ Fatal events were considered of cardiovascular causes when ICD codes 359-422 were present on the death certificates. In the present study 2387 people with complete data on the CRS, glucose variables, and follow up were included. Informed consent was obtained from all participants and the local ethics committee approved the study.

Measurements

Participants attended for a standard 75 g oral glucose tolerance test (OGTT) and a clinical examination that included a medical questionnaire and standard anthropometric measurements. Glucose was measured by the glucose

Abbreviations: BMI, body mass index; CRS, Cambridge risk score; ICD-9, ninth revision of the international classification of diseases; HbA_{1c}, glycated haemoglobin; WHR, waist-hip-ratio; OGTT, oral glucose tolerance test; WHO, World Health Organisation;

Table 1 Characteristics of participants in the Hoorn Study according to screening status

	True negative (n=1106)	False negative (n=41)	False positive (n=1037)	True positive (n=113)
Age (y)	58.9 (6.7)	60.4 (6.1)*	63.8 (7.1)†	65.9 (7.0)
Sex (M/F) (n)	428/678	11/30*	563/474	67/46
Family history of diabetes melitus (%)	13.6	22	26.0	34.5
Prescribed steroids (%)	0.1	0	2.3	3.5
Prescribed antihypertensives (%)	4.7	4.9*	32.2†	43.4
Weight (kg)	69.6 (9.3)	71.4 (8.6)*	80.8 (10.5)†	83.8 (12.7)
BMI (kg/m ²)	24.4 (2.2)‡	25.5 (2.3)*	28.4 (3.3)†	29.5 (3.9)
WHR	0.85 (0.08)‡	0.89 (0.09)*	0.93 (0.08)†	0.97 (0.07)
Systolic blood pressure (mmHg)	129 (18)‡	145 (22)	140 (20)†	148 (21)
Diastolic blood pressure (mmHg)	80 (10)‡	84 (12)	84 (10)†	86 (10)
Current smoker (%)	26.9	22	38.2†	26.5
Fasting glucose (mmol/l)	5.3 (0.5)‡	7.8 (2.8)	5.5 (0.5)†	8.0 (2.7)
2 hr glucose (mmol/l)	5.2 (1.5)‡	11.6 (5.4)	5.9 (1.7)†	13.4 (5.8)
HbA _{1c}	5.3 (0.5)‡	6.0 (1.4)	5.4 (0.5)†	6.5 (1.7)
Cholesterol (mmol/l)	6.6 (1.2)	6.8 (1.3)	6.7 (1.2)	6.7 (1.3)
HDL cholesterol (mmol/l)	1.4 (0.4)	1.3 (0.3)*	1.3 (0.3)†	1.2 (0.3)
LDL cholesterol (mmol/l)	4.60 (1.10)	4.56 (1.27)	4.68 (1.11)	4.47 (1.21)
Triglycerides (mmol/l)	1.25 (1.21 to 1.28)‡	1.72 (1.44 to 2.06)	1.53 (1.48 to 1.57)†	1.96 (1.79 to 2.15)
Fasting specific insulin (pmol/l)	68.53 (66.92 to 70.18)‡	94.67 (80.88 to 110.81)	86.30 (84.05 to 88.60)†	108.70 (100.34 to 117.76)

Data are mean (SD), geometric mean (95% CI) (triglycerides, insulin), and n (%).

* $p < 0.05$, false negative significantly different from true positive; † $p < 0.05$, false positive significantly different from true positives; ‡ $p < 0.05$ true negatives significantly different from false negatives.

dehydrogenase method (Merck, Darmstadt, Germany). Blood alcohol was determined by ion exchange high performance liquid chromatography using a modular diabetes monitoring system (Bio-Rad, Veenendaal, the Netherlands). Fasting specific insulin was measured with an insulin specific double antibody radioimmunoassay (antibody SP21; Linco, St Louis, MO). Serum total cholesterol, high density lipoprotein cholesterol, and triglycerides were measured with enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany).

The CRS was developed to predict undiagnosed type 2 diabetes with a logistic regression model.⁴ The CRS was based on the sum of the coefficients of the variables included in the model, age, sex, prescribed antihypertensive medication and steroids, family history of diabetes, body mass index (BMI), and smoking (see appendix). The cut off point of 0.199 with optimal sensitivity (77.3%) and specificity (72.0%) in the test population⁴ was used to calculate sensitivity and specificity in our study.

Statistical analyses

The fasting and 2 hour glucose concentrations were used to classify each participant into glucose tolerance categories according to the 1999 WHO diagnostic criteria.¹⁰ People who reported being treated for diabetes (diet, oral hypoglycaemic agents, or insulin) were classified as having known diabetes. The screening status of participants was classified as true negative, false negative, false positive, and true positive with the OGTT as a gold standard. Anthropometric and biochemical characteristics were compared between groups with the Student's *t* test comparison for normally distributed variables. Variables with skewed distributions were log transformed and a *t* test was applied to the log transformed data (triglyceride). Linear regression analysis was used to adjust comparisons for age, sex, or BMI. To study 10 year survival, Kaplan-Meier curves were plotted according to screening status. Cox's proportional hazards regression analysis was used to assess the association between screening status and mortality. All analyses were performed with the SPSS for Windows software, version 10.0.

RESULTS

The sensitivity and specificity of the CRS for the diagnosis of diabetes using the previously reported cut off point of 0.199 were 73% (95% confidence interval (95% CI) 66 to 80) and

52% (95% CI 50 to 54), respectively. About 50% of the study population had a high score on the CRS. Table 1 shows anthropometric and clinical characteristics of participants stratified by screening status. The false negative participants were significantly younger and were more likely to be female than the true positive participants. Also, the false negatives had significantly lower weight, BMI, and waist-hip ratio (WHR).

The false positive people were older than either of the two screen negative groups and they were markedly more obese. This group also included a higher proportion of cigarette smokers and a higher proportion of people who used antihypertensive medication. Also, the number of people with impaired glucose metabolism was higher in the false positive group than the true negative group; 270 (26%) and 134 (12%), respectively. The biochemical characteristics of the

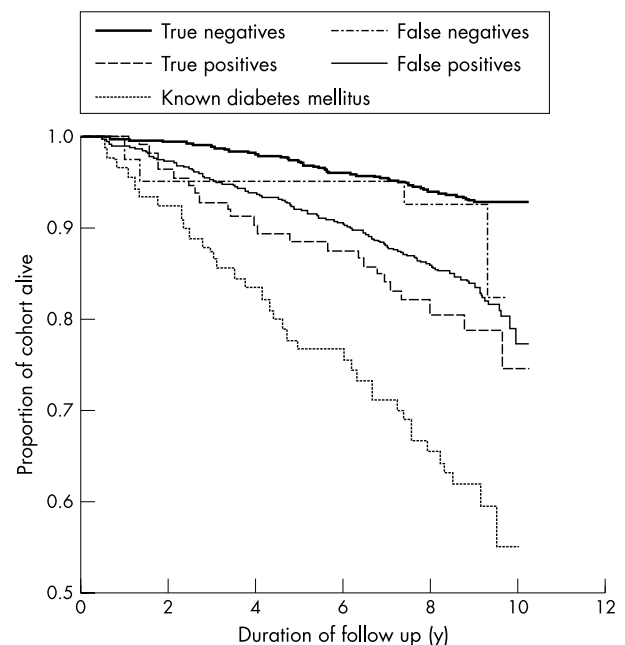


Figure 1 Kaplan-Meier curves according to screening status, with the survival curve of the known diabetic patients as a reference (Hoorn study).

Table 2 Mortality, incidence, and relative risk according to screening status: all cause mortality in the Hoorn study

	True negative (n=1106)	False negative (n=41)	False positive (n=1037)	True positive (n=113)
All events (n)	75	4	175	24
Incidence*	7.9	11.7	20.5	26.5
Cardiovascular disease events (n)	23	2	72	9
RR, unadjusted	1	1.50 (0.55 to 4.09)	2.62 (2.00 to 3.43)	3.40 (2.15 to 5.38)
RR, age and sex adjusted	1	1.52 (0.56 to 4.16)	1.56 (1.17 to 2.07)	1.73 (1.08 to 2.78)

*Incidence/1000 person-years

false positive group suggest that they had fewer of the features of the insulin resistance syndrome as their blood pressure, glucose, triglyceride, and fasting insulin concentrations were all lower than those in the true positive group. The differences in blood pressure, high density lipoprotein cholesterol, and triglycerides between the false and true positive group were also significant after adjustment for age, sex, and BMI. Although the false and true positive people were readily distinguishable on the basis of biochemical testing, their risk of mortality was very similar as shown in figure 1.

The incidence and relative risk of mortality in each group are shown in table 2. During follow up 278 people died and 63% of deaths occurred in the false positive group and 1.4% in the false negative group. Although the relative risk is highest in the true positive group, only 9% of deaths occurred in this category. Kaplan-Meier survival curves (fig 1) show that patients with known diabetes had the worst prognosis but survival in the false positive group was comparable with survival in the true positive group. Risk of mortality was higher in the false negative, false positive, and true positive groups than in the true negative group (table 2). Adjustment for age and sex resulted in similar risk estimates for all three groups, but risk of mortality was significantly higher only in the false positive and true positive groups compared with the true negative group.

DISCUSSION

The CRS is a simple instrument for identifying people at risk of having prevalent but undiagnosed diabetes using routinely available data. In the Hoorn population, a screening programme that used this score with subsequent biochemical testing in high risk people would successfully identify 73% of those who truly had diabetes. These screen detected people might benefit from early detection and prompt treatment of their diabetes and related risk factors, but trial evidence to support this assumption is still lacking.² However, this study suggests that screening with the CRS results in the identification of people with increased risk of mortality, whether or not they are subsequently shown to have diabetes on biochemical testing. There is, therefore, a large group of people who are screen positive and have increased risk of mortality, but do not have diabetes.

In this study, people with previously diagnosed type 2 diabetes had the highest risk of mortality. Other studies have also shown that the risk of mortality in known diabetic patients is high compared with non-diabetic people or newly diagnosed diabetic patients.¹¹⁻¹² Most of the patients with previously diagnosed diabetes in this study were on treatment to lower blood glucose. The high mortality risk in this group shows the need to target action at improving care for people known to have type 2 diabetes.

The false negative population in which the risk of mortality is not significantly increased, are a relatively small group of lean and young people who have diabetes but who were not identified as being at risk by the CRS. This group of missed

patients does not fit the classic anthropometric stereotype and may include people in whom the primary pathogenetic defect is β cell dysfunction rather than insulin resistance. As they lack the risk factors that are integrated into the CRS or other targeted screening approaches, these people would only be detectable by universal screening with glucose testing. The natural history of diabetes in relatively lean people is unclear and it may be that if undetected they would progress more rapidly from asymptomatic hyperglycaemia to symptomatic diabetes. If so, these false negative people may come to clinical recognition swiftly despite the fact that they would have been missed by the screening procedure.

In our study, the false positive group constitutes half of the population. In current screening practice this large group of people would be sent home feeling reassured about diabetes but unaware of their increased risk of mortality. Given that 63% of the total number of deaths occur in this subgroup, it may be of greater public health benefit to intervene in the screen positive population as a whole rather than only in the relatively small group who on subsequent biochemical testing have an increased glucose concentration. The United Kingdom National Screening Committee, who are currently considering screening for type 2 diabetes, have defined screening as "the systematic application of tests or inquiries to identify people at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action".¹³ The results of this study suggest that direct preventive action in the screen positive group as a whole may be an appropriate strategy.

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Appendix: The Cambridge risk score

	Risk score	Characteristic
α	-6.322	Constant
$\beta 1X1$	-0.879	Female
$\beta 2X2$	1.222	Prescribed antihypertensive medication
$\beta 3X3$	2.191	Prescribed steroids
$\beta 4X4$	0.063	Age (y)
$\beta 5X5$	0	BMI<25
	0.699	BMI=25 to 27.49
	1.970	BMI=27.50 to 29.99
	2.518	BMI \geq 30
$\beta 6X6$	0	No first degree relative had diabetes
	0.728	Parent or sibling had diabetes
	0.753	Parent and sibling had diabetes
$\beta 7X7$	0	Non-smoker
	-0.218	Ex-smoker
	0.855	Current smoker

Probability of having type 2 diabetes:
 $1/1+e^{-[\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5+\beta 6X6+\beta 7X7]}$

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