

# Routinely collected general practice data aids identification of people with hyperglycaemia and metabolic syndrome

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## Abstract

**Aims** To assess the performance of a risk score comprising data routinely available in general practice records (age, gender, body mass index, family history of diabetes, smoking habits and prescribed anti-hypertensive drugs or steroids) in detecting diabetes, impaired glucose tolerance and metabolic syndrome.

**Methods** In a population-based, cross-sectional study in a semi-rural general practice in Jutland, Denmark, Cambridge Risk Scores were calculated for 1355 patients without known diabetes (69% response rate) who completed questionnaires and underwent anthropometric measurement and an oral glucose tolerance test.

**Results** Prevalences of diabetes, impaired glucose tolerance and metabolic syndrome were 2.29% (95% CI: 1.56–3.23), 6.64% (95% CI: 5.38–8.10) and 13.4% (95% CI: 11.5–15.2), respectively. Area under the ROC curve for the risk score and diabetes was 83.8% (75.9–91.7) and for metabolic syndrome [European Group for the Study of Insulin Resistance (EGIR)] was 78.1% (74.6–81.6). Twenty per cent of the population had a risk score above 0.246; at this threshold the sensitivity to detect diabetes was 71.0% (53.4–83.9), the specificity 81.2% (79.0–83.2), positive predictive value 8.1% (6.6–10.0) and likelihood ratio 3.77 (2.94–4.85). For metabolic syndrome (EGIR) corresponding values for sensitivity were 50.3% (43.1–57.5), specificity 84.7% (82.5–85.6), positive predictive value 33.6% (28.2–39.4), and likelihood ratio 3.28 (2.69–4.00).

**Conclusions** Undiagnosed hyperglycaemia and metabolic syndrome are common. The Cambridge Risk Score is a practical first step in a screening procedure to identify individuals with these disorders who might benefit from diagnostic testing or to direct preventive interventions.

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**Keywords** general practice, metabolic syndrome, risk score, screening, Type 2 diabetes

**Abbreviations** CRS, Cambridge Risk Score; EGIR, European Group for the Study of Insulin Resistance; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; WHO, World Health Organization

## Introduction

There remains considerable uncertainty over whether mass population screening for diabetes would be beneficial [1,2]. Targeted screening among high-risk groups is more likely to be cost-effective [3–5]. However, as a majority of the adult

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population have at least one recognized risk factor for diabetes [6], the identification of those most likely to have prevalent undiagnosed diabetes is problematic. People at increased risk of developing Type 2 diabetes, such as those with impaired fasting glycaemia (IFG), impaired glucose tolerance (IGT) and metabolic syndrome (MetS) also form a group with high cardiovascular risk [7]. Recent trials demonstrate that Type 2 diabetes can be prevented in people with IGT through behavioural interventions [8,9], but identification of these individuals by population screening using an oral glucose tolerance test (OGTT), as occurred in these trials, is not currently feasible in primary care. Practical strategies are therefore needed to identify manageable numbers of patients at high risk of having diabetes, developing diabetes or developing the complications of diabetes, in particular cardiovascular disease (CVD).

Several questionnaires have been developed to identify people with prevalent undiagnosed diabetes [10–13]. However, their distribution and analysis create an administrative burden for primary care teams, and they demand the participation of the patient, which may create anxiety and false reassurance [14,15]. The Cambridge Risk Score (CRS) uses data routinely recorded in many general practice surgeries (age, gender, height, weight, prescription of steroid and anti-hypertensive medication, family and smoking history) and has already been demonstrated to identify individuals with undiagnosed prevalent diabetes in different ethnic groups and to predict mortality [16–18]. We aimed to test the performance of the score in a Danish general practice population in identifying people with undiagnosed diabetes, impaired glucose tolerance, impaired fasting glycaemia and metabolic syndrome who might form an appropriate target group for preventive interventions. We chose to use the European Group for the Study of Insulin Resistance (EGIR) and the National Cholesterol Education Program (NCEP) definitions of MetS for these assessments, as the World Health Organization (WHO) definition is not appropriate for general practice use (insulin resistance has to be measured by a clamp technique, which is very resource intensive). We did not aim to compare the two definitions of MetS in this study.

## Patients and methods

### Study setting and population

The study was set in a single, semi-rural general practice in central Jutland, Denmark (two partners, 3108 registered patients). The area is mainly agricultural but many people work in nearby towns. The overall unemployment rate is low and the patients registered with the practice have an age and gender distribution similar to the Danish population. The investigator (PEH) has a special interest in diabetes care and research. The design of the study has been previously described [19]. In brief, from April 1998 to June 2000 all 2082 patients (1057 male and 1025 female) aged 20–69 years were invited to participate in a study to assess the prevalence of metabolic syndrome and undiagnosed Type 2 diabetes. One hundred and twelve people were excluded because they had insulin-treated diabetes, severe

mental or physical illness or were moving away before the examination (63 male and 49 female). Five hundred and ninety-six people (310 male, 286 female) declined to participate, 1374 people gave written informed consent and were examined. Among these, 19 patients with known diet- or tablet-treated Type 2 diabetes were excluded from the analyses. Thus, 1355 people were assessed and included in the analysis, an effective response rate of 69% (1355/1951).

### Assessments

After a 10-h overnight fast, a standard OGTT with 75 g of glucose (Glucodex®, Rougier, Chambly, QC, Canada) was performed between 06.00 and 09.00 h [20]. Participants were instructed not to drink, eat, smoke tobacco, or take any medication during the fasting period and the test. The investigator (PEH) carried out the physical examination of all participants, unaware of the blood test results. Weight in underwear was measured to the nearest 100 g (Seca® Electronic 0–200 kg). Height without shoes was measured to the nearest 0.5 cm. Waist circumference was measured in the umbilical plane to the nearest cm. Blood pressure was measured according to standard protocol to the nearest 2 mmHg (Hawksley Random Zero Mk II Mercury Sphygmomanometer). Self-administered questionnaires requested information on smoking habits, medication and family history of diabetes and cardiovascular disease in first-degree relatives.

### Biochemical methods

Insulin was analysed at the Department of Endocrinology, Odense University Hospital, Denmark using double-antibody technique (AutoDELFIA™, Wallac Oy, Turku, Finland). Other analyses were carried out at the Department of Clinical Biochemistry, Viborg Hospital, Denmark. Total cholesterol and triglycerides were analysed using a colourimetric test (Vitros Ektachem 950 IRC, Rochester, NY, USA), HDL cholesterol (Liquid-N-geneous HDL-C, RA 1000; Genzyme, Terrytown, NY, USA). LDL cholesterol was calculated using Friedewald's formula [21]. Whole blood was stabilized with EDTA for analysis of glycated haemoglobin (HbA<sub>1c</sub>) (HPLC Variant™; Bio-Rad Laboratories, Hercules, CA, USA). Within 5 min of drawing the sample, EDTA-stabilized whole blood was also added to a haemolysate buffer to stop glucose metabolism and analysed for glucose within 5 h (enzymatic amperometric test, EBIO Eppendorf-Netheler-Hinz GmbH) (CV 3.3%). All blood glucose analyses were undertaken on two separately collected samples. Each of the two samples was analysed separately, and the results are reported as the mean of the two measurements.

### Statistical analyses

Participants were grouped according to their test results into the following categories: (i) Type 2 diabetes alone; (ii) impaired glucose regulation (Type 2 diabetes or IGT or IFG); (iii) MetS (EGIR; MetS<sub>EGIR</sub>) and MetS (NCEP; MetS<sub>NCEP</sub>).

The Cambridge Risk Score was calculated for all participants (the variables included in the score and corresponding beta-coefficients are shown in the Appendix). Sensitivity, specificity,

positive and negative predictive values, and likelihood ratios of positive tests with 95% confidence intervals were calculated for selected risk score thresholds, representing between 10 and 50% of the population requiring diagnostic testing following a positive risk score. The confidence intervals for the likelihood ratios were calculated using the Log method. Receiver operating characteristic (ROC) curves were generated, and the area under the curves (AUC) and 95% confidence intervals were used to assess the performance of the risk score. All analyses were undertaken using SPSS 11.0 for Windows® (SAS, Cary, NC, USA) and Statistics with Confidence, 2nd edition [22]. The study was carried out according to the Declaration of Helsinki and was approved by the regional Research Ethics Committee.

## Results

The study population characteristics are shown in Table 1. People who declined to participate were younger than those examined [mean age 40.2 (SD 13.9) years vs. 44.1 (SD 12.7) years, respectively,  $t = 5.901$ ,  $P < 0.001$ ]. There was no statistically significant difference in gender between responders and non-responders.

Thirty-one participants had previously undiagnosed diabetes (2.29%, 95% CI: 1.56–3.23), 141 had pre-diabetes (WHO definition), i.e. 90 had impaired glucose tolerance (6.64%, 95% CI: 5.38–8.10), 51 had impaired fasting glycaemia (3.76%, 95% CI: 2.81–4.91), 181 had metabolic syndrome (MetS<sub>EGIR</sub>; 13.4%, 95% CI: 11.50–15.20) and 152 had metabolic syndrome (MetS<sub>NCEP</sub>; 11.2%, 95% CI: 9.54–12.90).

The performance of the risk score in identifying people with prevalent undiagnosed Type 2 diabetes, impaired glucose

regulation and the metabolic syndrome (MetS<sub>EGIR</sub> and MetS<sub>NCEP</sub>) is shown in Tables 2 and 3. Figure 1 shows the ROC curves for the performance of the risk score in identifying those with undiagnosed diabetes, impaired glucose regulation and metabolic syndrome (MetS<sub>EGIR</sub> and MetS<sub>NCEP</sub>). The area under the curves were, respectively, 83.8% (95% CI 75.9–91.7), 74.0% (69.9–78.0), 79.0% (75.7–82.4), and 80.1% (76.8–83.4). Using a risk score threshold of 0.246, 271 participants (20% of the population) would have required further testing and 22 (71%) people with prevalent undiagnosed diabetes, 59 (42%) with IGT or IFG, 81 (47.1%) with impaired glucose regulation, and 91 (50.3%) with MetS<sub>EGIR</sub> and 78 (51.3%) with MetS<sub>NCEP</sub> would have been detected.

## Discussion

Metabolic syndrome and disorders of glucose metabolism are common in the Danish population and compare with similar data from other settings [23]. Thirty-one people with Type 2 diabetes were detected through screening, underlining the high prevalence of undiagnosed disease. Combining routinely available data such as the risk factors in the Cambridge Risk Score appears to work well in identifying people with previously undiagnosed diabetes in a Danish general practice population. It also performs reasonably well in identifying people with impaired fasting glycaemia, impaired glucose tolerance and the metabolic syndrome. These individuals are at increased risk of developing diabetes and cardiovascular disease and therefore constitute a group for whom preventive interventions might be cost-effective [7,24]. Calculation of risk scores automatically using electronic medical records followed by

**Table 1** Characteristics of study participants according to glucose tolerance (WHO criteria 1999)

	NGT	IFG/IGT	T2DM	P for trend*
<i>n</i> = 1355	1183	141	31	
Female (%)	50.3	48.2	38.7	0.411
Age (years)	43.4 (12.3)	50.1 (13.0)	57.0 (9.5)	< 0.001
Fasting glucose (mmol/l)	4.69 (0.35)	5.26 (0.52)	6.86 (1.76)	< 0.001
HbA <sub>1c</sub> (%)	5.55 (0.45)	5.79 (0.45)	6.78 (1.16)	< 0.001
Total cholesterol (mmol/l)	5.24 (1.02)	5.55 (1.03)	6.16 (1.78)	< 0.001
Triglycerides (mmol/l)	1.41 (0.83)	1.77 (0.91)	2.74 (1.72)	< 0.001
Systolic BP (mmHg)	120 (16.5)	130 (20.8)	140 (19.2)	< 0.001
Waist circumference, female (cm)	84 (11.7)	93 (14.5)	102 (10.4)	< 0.001
Waist circumference, male (cm)	93 (10.4)	100 (10.7)	110 (17.5)	< 0.001
Body mass index (kg/m <sup>2</sup> )	25.3 (4.3)	28.3 (5.9)	32.2 (6.9)	< 0.001
Current smoker (%)	35.4	30.5	29.0	0.394
Anti-hypertensive treatment (%)	7.9	19.9	38.7	< 0.001
Hypertension or treatment (%)†	21.2	46.8	77.4	< 0.001
Steroid treatment	1.0	2.8	6.5	0.008
Dyslipidaemia or treatment‡	16.7	34.0	64.5	< 0.001
Family history of DM (parent and/or sibling)	16.9	34.8	36.0	< 0.001

DM, diabetes mellitus; NGT, normal glucose tolerance; T2DM, Type 2 diabetes mellitus.

\*One way ANOVA or Kruskal–Wallis test.

†Defined as either systolic blood pressure (BP)  $\geq 140$  mmHg, or diastolic BP  $\geq 90$  mmHg, or treatment for hypertension.

‡Defined as either HDL  $\leq 1.0$  mmol/l, or triglycerides  $> 2.0$  mmol/l, or treatment for dyslipidaemia.

Data are presented as mean (SD) unless specified.

**Table 2** Performance of the Cambridge Risk Score (CRS) in identifying metabolic syndrome

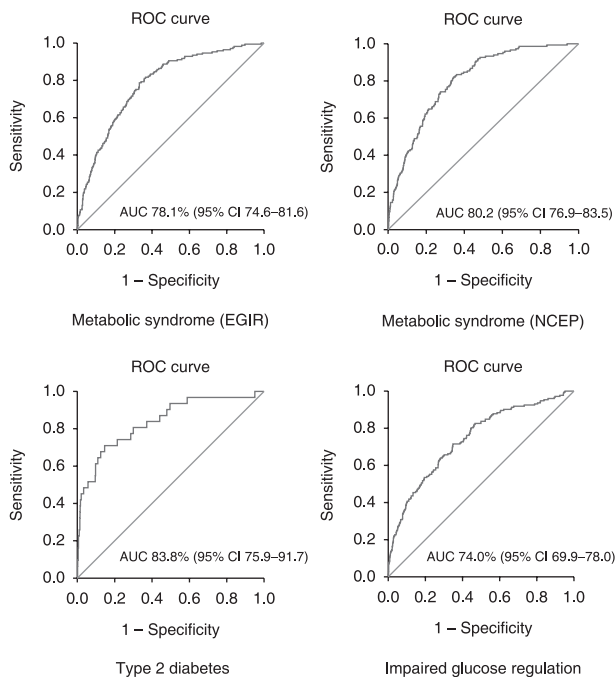
% of population above threshold	CRS threshold	Metabolic syndrome (EGIR)					Metabolic syndrome (NCEP)				
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)
50	0.058	87.3 (81.7–91.4)	55.7 (52.9–58.5)	22.3 (20.3–26.6)	96.6 (95.0–97.7)	1.97 (1.81–2.15)	88.2 (82.1–92.4)	54.8 (52.0–57.6)	19.8 (17.4–22.4)	97.3 (95.8–98.3)	1.95 (1.79–2.12)
40	0.086	79.6 (73.1–84.8)	66.1 (63.3–68.8)	26.6 (23.0–30.4)	95.4 (93.8–96.7)	2.35 (2.11–2.62)	82.2 (75.4–87.5)	65.3 (62.6–68.0)	23.0 (20.5–25.7)	96.7 (95.2–97.7)	2.37 (2.13–2.64)
30	0.143	66.3 (59.1–72.8)	75.6 (73.1–78.0)	29.6 (25.3–34.2)	93.6 (91.8–95.0)	2.72 (2.36–3.15)	69.1 (61.3–75.9)	74.9 (72.5–77.3)	25.8 (23.2–28.6)	95.0 (93.5–96.3)	2.76 (2.39–3.19)
20	0.246	50.3 (43.1–57.5)	84.7 (82.5–86.6)	33.6 (28.2–39.4)	91.7 (89.9–93.2)	3.28 (2.69–4.00)	51.3 (43.9–59.1)	84.0 (81.8–85.9)	28.8 (26.1–31.7)	93.2 (91.5–94.5)	3.20 (2.61–3.91)
10	0.428	31.5 (25.2–38.6)	93.4 (91.8–94.6)	42.2 (34.2–50.7)	89.8 (88.0–91.4)	4.74 (3.50–6.42)	30.9 (24.1–38.7)	92.6 (91.1–94.0)	34.5 (31.6–37.5)	91.4 (89.7–92.8)	4.23 (3.10–5.47)

LR+, likelihood ratio for a positive test; NPV, negative predictive value; PPV, positive predictive value.

**Table 3** Performance of the Cambridge Risk Score (CRS) in identifying impaired glucose regulation (diabetes, IFG and IGT) and Type 2 diabetes

% of population above threshold	CRS threshold	Impaired glucose regulation					Type 2 diabetes				
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)
50	0.058	80.2 (73.6–83.5)	54.4 (51.5–57.2)	20.4 (18.0–23.0)	95.0 (93.1–96.4)	1.76 (1.60–1.94)	90.3 (75.1–96.7)	50.9 (48.2–53.6)	4.1 (3.0–5.5)	99.6 (98.7–99.8)	1.84 (1.62–2.09)
40	0.086	71.5 (64.4–77.7)	64.6 (61.8–67.3)	22.7 (20.2–25.4)	94.0 (92.1–95.4)	2.02 (1.79–2.28)	83.9 (67.2–92.9)	61.0 (58.4–63.6)	4.8 (3.6–6.3)	99.4 (98.6–99.7)	2.15 (1.82–2.55)
30	0.143	58.7 (51.3–65.8)	74.2 (71.6–76.6)	24.8 (22.2–27.6)	92.5 (90.7–94.0)	2.28 (1.94–2.67)	77.4 (60.2–88.6)	71.1 (68.6–73.5)	5.9 (4.6–7.5)	99.3 (98.5–99.6)	2.68 (2.18–3.30)
20	0.246	47.1 (39.8–54.5)	83.9 (81.7–85.9)	29.8 (27.0–32.7)	91.6 (89.8–93.1)	2.93 (2.39–3.60)	71.0 (53.4–83.9)	81.2 (79.0–83.2)	8.1 (6.6–10.0)	99.2 (98.4–99.6)	3.77 (2.94–4.85)
10	0.428	30.8 (24.4–38.1)	93.1 (91.5–94.4)	39.0 (36.0–42.1)	90.2 (88.5–91.8)	4.45 (3.27–6.04)	51.6 (34.8–68.0)	91.0 (89.4–92.4)	11.7 (9.9–13.8)	98.8 (98.0–99.3)	5.74 (3.92–8.41)

LR+, likelihood ratio for a positive test; NPV, negative predictive value; PPV, positive predictive value.



**Figure 1** Receiver operating characteristics (ROC) of the Cambridge Risk Score for identifying metabolic syndrome (EGIR), metabolic syndrome (NCEP), Type 2 diabetes and impaired glucose regulation.

diagnostic testing on a proportion of the population is a more practical approach for primary care teams to identify those at risk than inviting all adults for blood glucose estimation.

The study was undertaken in a general practice population and there was a 69% response rate, so the estimates of the performance of the risk score are unlikely to exhibit spectrum bias. The study population was broadly representative of the Danish population, although non-attenders were younger than participants. Given the lower prevalence of diabetes and metabolic syndrome among younger people, the reported positive predictive values may therefore have been slightly overestimated. However, this discrepancy between responders and non-responders was largely restricted to the 20–29 and 30–39 year age groups, in which few patients were found to have abnormal test results. In the 40–69 years age group, the likely target group for invitation to screening, the mean ages of responders and non-responders were very similar [53.0 (SD 8.4) and 53.3 (SD 9.1) years, respectively,  $t = 0.573$ ,  $P = 0.567$ ]. Non-attenders for screening are frequently at higher absolute risk than attenders [25]. The positive predictive value of the risk score might therefore have been enhanced if those who had declined the offer of screening had agreed to be examined.

The diagnostic categories were based upon the results of a single glucose tolerance test, which is justifiable in epidemiological research, but less so in everyday clinical settings. Consequently, some misclassification of participants is inevitable as a result of test–retest discrepancies [26,27]. Risk of myocardial infarction and death rises more or less linearly with

increasing blood glucose levels in the general and diabetic populations [28,29]; consequently, even if some people were misclassified they would still remain in a high-risk group. Not all patients' records will contain information on the risk score variables. However, the risk score has been shown to perform almost as well when data are missing for smoking and family history [30]. Furthermore, missing data for height and weight could be collected by telephone, questionnaire or opportunistically. Body mass index calculated using self-reported height and weight provides a reasonable approximation of measured body mass index [31,32].

It is clear that when people are tested and given the label 'impaired glucose tolerance', many benefit from subsequent intervention. It remains to be seen whether communication of risk score information followed by similar interventions would produce equivalent health gain. In addition to the two definitions of MetS used in this paper, the International Diabetes Federation have recently published a new set of diagnostic criteria, including a lowering of the glucose threshold, resulting in more people being given the label of MetS. Future research might clarify which set of criteria for defining the metabolic syndrome will best predict metabolic and related cardiovascular outcomes. There is little data on the adverse consequences of risk assessment and attribution of a diagnostic label and the extent of false reassurance in those deemed to be below specific, and somewhat arbitrary, thresholds. Inappropriate labelling of healthy people by uncritically lowering thresholds for biochemical or physiological measurements should be avoided [33]. It is important to remain aware of the ethical differences between screening and clinical care. In the present survey, all results were sent by letter to the participants, and those with values outside the reference intervals were requested to see their doctor. If the patient attended, a discussion took place concerning which results were to be entered into the medical record. If the patient did not attend no results were entered.

The Cambridge Risk Score, and similar tools, do not entail biochemical testing or the distribution and analysis of questionnaires. Rather, they utilize information that has already been collected for many individuals in countries with well-developed primary care. Use of such pre-screening instruments will inevitably reduce the overall sensitivity of a screening programme, but might also reduce costs, both economic and psychological, including the potential for false reassurance among those testing negative. The risk score appears to identify individuals with a range of metabolic disturbances related to glucose regulation and risk of cardiovascular disease and premature death [16]. There is growing evidence that the burden of disease may be reduced among such individuals through behavioural and pharmacological interventions [8,9]. If screening is justified, then one approach might be to use a pre-screening instrument as a first step, with the aim of reducing the number of people requiring further testing or direct preventive activity. General practitioners should therefore be encouraged to collect and record the risk factors information

necessary to calculate such simple and easily applied predictive models.

## Competing interests

Pfizer A/S Denmark sponsored the Hawksley sphygmomanometer, and Bayer A/S sponsored Glucodex® for the OGTTs.

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## Appendix

Table 1A The Cambridge Risk Score\* [30]

	$\beta$ coefficient	Characteristic
$\alpha$	-6.322	Constant
$\beta_1$	-0.879	Female
$\beta_2$	1.222	Prescribed anti-hypertensive medication
$\beta_3$	2.191	Prescribed steroids
$\beta_4$	0.063	$x$ age in years
$\beta_5$	0.000	Body mass index < 25.0 kg/m <sup>2</sup>
	0.699	Body mass index = 25.0–27.49 kg/m <sup>2</sup>
	1.970	Body mass index = 27.5–29.99 kg/m <sup>2</sup>
	2.518	Body mass index $\geq$ 30 kg/m <sup>2</sup>
$\beta_6$	0.000	No first-degree relatives had diabetes
	0.728	Parent or sibling had diabetes
	0.753	Parent and sibling had diabetes
$\beta_7$	0.000	Non-smoker
	-0.218	Ex-smoker
	0.855	Current smoker

\*Probability of having Type 2 diabetes =  
 $1/1 + e^{-(\alpha + \beta_1 \times 1 + \beta_2 \times 2 + \beta_3 \times 3 + \beta_4 \times 4 + \beta_5 \times 5 + \beta_6 \times 6 + \beta_7 \times 7)}$