The Performance of a Risk Score in Predicting Undiagnosed Hyperglycemia

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OBJECTIVE — Type 2 diabetes is a serious disease that is commonly undetected and for which screening is sometimes advocated. A number of risk factors are associated with prevalent undiagnosed diabetes. The use of routinely available information on these factors has been proposed as a simple and effective way of identifying individuals at high risk for having the disease. The objective of this study was to assess the effectiveness of the Cambridge risk score in a large and representative population.

RESEARCH DESIGN AND METHODS — A risk score derived from data in a previous study was tested for its ability to detect prevalent undiagnosed hyperglycemia as measured by a GHb ≥6.0, 6.5, or 7% in 6,567 subjects aged 39–78 years in the European Prospective Investigation of Cancer—Norfolk cohort.

RESULTS — For a specificity of 78%, the risk score predicted a GHb of ≥7.0% in subjects aged 39–78 years, with a sensitivity of 51% (95% CI 40–62). The areas under the receiver-operating characteristic (ROC) curve for GHb ≥6.0, 6.5, and 7% were 65.7% (63.8–67.6), 71.2% (68.4–75.2), and 74.2% (69.5–79.0), respectively. The area under the ROC curve was not significantly reduced if data on family and smoking history were unavailable for any of the cut-offs for GHb.

CONCLUSIONS — The risk score performed as well as other previously reported models in all age groups. We concluded that a simple risk score using data routinely available in primary care can identify people with an elevated GHb with reasonable sensitivity and specificity, and it could therefore form part of a strategy for early detection of type 2 diabetes.

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Type 2 diabetes is a common and serious disease (1,2) that places a heavy burden on health services through the treatment of its complications (3). It is estimated that 50% of diabetes cases remain undetected (2), yet at diagnosis many diabetic patients exhibit signs of micro- and macrovascular complications (4–6). In the absence of a formal screening program, methods for identifying cases of diabetes remain haphazard, but could be improved by targeting those at highest risk (7,8). Information on many known risk factors for diabetes (e.g., age, sex, prescribed medication, smoking) is already available as routine clinical data, particularly in countries with well-developed primary health care systems (9). A risk score using such data from routine records has been developed and tested in the U.K. and appears to be effective in identifying people with undiagnosed diabetes (10).

In this study, we tested the performance of the risk score in detecting prevalent undiagnosed hyperglycemia, as defined by GHb (HbA1c) measurement in a large, population-based cohort from the European Prospective Investigation of Cancer (EPIC)—Norfolk study. Because information on some risk factors may be incomplete in general practice records, the risk score was also tested after excluding some components. Finally, we compared the performance of the risk score against that of a predictive model developed in Holland (11).

RESEARCH DESIGN AND METHODS

Development and preliminary evaluation of the risk score

The development and evaluation of the risk score have been previously described (10). In brief, a predictive score was produced using stepwise logistic regression on data from a study of incident cases of clinically diagnosed type 2 diabetes (the Wessex study) (12) and a study of prevalent cases of detected diabetes detected through screening (the Ely study) (13). The variables used in the risk score were age, sex, prescribed medication (steroid and antihypertensive), smoking, family history, and BMI. The parameters for the risk score are reproduced in the Appendix. The score was evaluated in an independent, randomly selected population sample from the Ely study who underwent oral glucose tolerance testing. The sensitivity, specificity, and area under the receiver-operating characteristic (ROC) curve were 82, 62, and 79.5 (95% CI 72.6–86.3), respectively.

Subjects and methods

The design of the EPIC-Norfolk study, including recruitment and measures, has been reported in full elsewhere (14). This study is a multicenter prospective cohort study examining the relation between dietary and other lifestyle factors and the risk of developing various chronic conditions, including cancer. Participants completed a detailed health and lifestyle questionnaire, including questions on current medication, smoking habits, and family history of diabetes. After the questionnaire, the subjects were invited for a health check-up at a general practice fa-
Table 1—Characteristics of the 6,567 people in the EPIC-Norfolk cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2,889</td>
<td>3,678</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.3 ± 9.2</td>
<td>58.7 ± 9.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.8 ± 6.5</td>
<td>160.9 ± 6.26</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.6 ± 11.4</td>
<td>67.9 ± 11.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.3 ± 9.7</td>
<td>82.5 ± 10.8</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>103.2 ± 6.5</td>
<td>103.7 ± 9.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.6 ± 17.0</td>
<td>133.2 ± 18.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.4 ± 10.6</td>
<td>81.0 ± 11.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 3.3</td>
<td>26.2 ± 4.3</td>
</tr>
<tr>
<td>Taking prescribed medication (%)</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Antidyslipidemia</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Steroid</td>
<td>12.0</td>
<td>13.6</td>
</tr>
<tr>
<td>First-degree relative with diabetes (%)</td>
<td>5.36 ± 0.71</td>
<td>5.31 ± 0.66</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise indicated.

The risk score in EPIC-Norfolk

The diabetes risk score was calculated for the entire sample. Sensitivity, specificity, predictive values, and likelihood ratios for detection of undiagnosed hyperglycemia were calculated for cut-offs of the risk score between 0 and 1. ROC curves were plotted, and area under the curve (AUC) values and their CIs were estimated using the nonparametric method described by Hanley and McNeil (19). The Statistical Package for the Social Sciences Program, Version 8.0 (SPSS), was used for analysis. CIs for the performance characteristics of the risk score were calculated using Confidence Interval Analysis software, version 1.0 (20).

The performance of the risk score was then estimated with data excluded for different variables in turn. First, family history was omitted, then family history and smoking history, then family history and BMI, and finally BMI, family history, and smoking history. Of the variables used by the risk score, BMI, family history, and smoking history were considered the most likely to be unavailable in routine clinical data.

The prediction model (PM1) developed by Baan et al. (11) in Holland was also applied to the entire EPIC sample; its performance in predicting an HbA1c ≥7% was compared with the risk score. The PM1 model is the only statistical risk model in the literature comparable with the Cambridge risk score, in that it uses routinely available risk factor data to predict undiagnosed diabetes. The other model developed by Baan et al. (PM2) showed a better performance in the original data (11), but it was not appropriate for comparison in this study, as it required information on regular bicycle use, which would not be routinely available or culturally appropriate in the U.K.

RESULTS — The characteristics of the 6,567 individuals in the EPIC sample are shown in Table 1. In all, 84 individuals (1.3%) had previously undiagnosed hyperglycemia, as defined by an HbA1c ≥7%. Age, hip circumference, BMI, family history of diabetes, and smoking habits were all significantly associated (P < 0.01) with an HbA1c ≥7%. The association of the risk score variables with previously undiagnosed hyperglycemia in the EPIC-Norfolk sample is shown in Fig. 1.

The performance of the risk score in the whole EPIC sample against a GHB
≥7% is shown in Table 2. For a specificity of 78%, sensitivity was 51% (CI 40–62). The AUC was 74.2% (69.5–79.0), slightly greater than the area for PM1 of Baan et al. (73.2%; 68.3–78.1). The ROC curves for the risk score and the PM1 in the whole sample are shown in Fig. 2.

When the diagnostic threshold for elevated GHb was lowered to 6.5%, the number of those with undiagnosed hyperglycemia rose to 203 (3.1%). The AUC values for the risk score and PM1 for this threshold were 71.8% (CI 68.4–75.2) and 70.7% (67.3–74.1), respectively. When the threshold for GHb was 6.0%, the number of those with undiagnosed hyperglycemia was 841 (12.8%). The AUC values for the risk score and PM1 for this threshold were 65.7% (63.8–67.6) and 64.3% (61.7–66.5), respectively.

When family history data were excluded from the risk score, the AUC actually rose to 75.1% (CI 68.5–81.7), although it was not significantly different from that of the original score. With smoking and family history excluded, the AUC rose further to 75.2% (68.7–81.7). With BMI and family history missing, the AUC for a threshold of 7% dropped significantly to 68.9% (63.7–74.1), and with BMI, smoking history, and family history excluded, the AUC was 69.8% (64.0–75.6). The performance of the risk score with missing variables was not significantly different from that of the original score for different thresholds of GHb (6.0 and 6.5%).

**CONCLUSIONS**

The performance of the risk score in EPIC-Norfolk

When tested in the EPIC cohort, a large, independent, and representative sample of the general population, the risk score performed reasonably well at identifying individuals at high risk for having undiagnosed hyperglycemia. The AUC value, the most useful comparative measure of the performance of screening tests (19), for the risk score in the EPIC population

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**Table 2—Performance of the risk score in predicting previously undiagnosed hyperglycemia (HbA1c ≥7.0%) in the EPIC study (n = 6,567)**

<table>
<thead>
<tr>
<th>Risk score cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Likelihood ratio of a positive test</th>
<th>Likelihood ratio of a negative test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.11</td>
<td>85 (75.8–92.2)</td>
<td>51 (49.7–52.1)</td>
<td>2.2 (1.7–2.7)</td>
<td>99.6 (99.4–99.8)</td>
<td>1.73 (1.56–1.91)</td>
<td>0.29 (0.13–0.46)</td>
</tr>
<tr>
<td>0.15</td>
<td>72 (60.9–81.3)</td>
<td>60 (58.8–61.2)</td>
<td>2.2 (1.8–3.0)</td>
<td>99.4 (99.1–99.6)</td>
<td>1.80 (1.54–2.06)</td>
<td>0.46 (0.30–0.64)</td>
</tr>
<tr>
<td>0.17</td>
<td>70 (58.4–79.2)</td>
<td>64 (62.7–65.0)</td>
<td>2.4 (1.8–3.1)</td>
<td>99.4 (99.2–99.6)</td>
<td>1.94 (1.65–2.24)</td>
<td>0.47 (0.31–0.63)</td>
</tr>
<tr>
<td>0.23</td>
<td>63 (52.0–73.8)</td>
<td>72 (70.8–73.0)</td>
<td>2.8 (2.1–3.6)</td>
<td>99.4 (99.1–99.6)</td>
<td>2.25 (1.86–2.64)</td>
<td>0.51 (0.36–0.67)</td>
</tr>
<tr>
<td>0.29</td>
<td>51 (39.9–62.4)</td>
<td>78 (77.3–79.3)</td>
<td>2.9 (2.1–3.9)</td>
<td>99.2 (99.0–99.5)</td>
<td>2.32 (1.80–2.83)</td>
<td>0.63 (0.48–0.77)</td>
</tr>
</tbody>
</table>

Data are % (CI).
was 74.2%. This was not significantly different from the AUC in the original evaluation, but it was slightly higher than the value for the closest comparable tool, the PM1 model of Baan et al. (11) for all thresholds of GHb that were tested.

Other groups, such as the American Diabetes Association (21), have developed questionnaires to combine risk factor data efficiently when identifying those at high risk of undiagnosed diabetes. The AUC for the risk score was higher than those reported for two risk factor questionnaires: the Herman et al. questionnaire (22) and the Ruige et al. questionnaire (23) in a sample of Dutch people aged 50–74 years (23). The risk score also has comparable performance (AUC) in detecting undiagnosed diabetes to some biochemical tests, including fasting capillary glucose (24), 1-h postprandial capillary glucose (25), random capillary glucose (25), and glycosuria testing (16). Although the questionnaires and biochemical tests were evaluated against the 2-h plasma glucose, a more widely accepted gold standard than the GHb used in this study, GHb has been shown to correlate well with the development of clinical outcomes characterizing diabetes, such as retinopathy (17,26). However, it has only recently been proposed as a diagnostic test for diabetes (17,27,28). There will inevitably be some variation in the individuals diagnosed with diabetes by glucose tolerance test and GHb. Nevertheless, this is unlikely to have had a large impact on the estimate of the performance of the risk score in the present cohort.

Given that the risk score uses existing patient information, it may have a useful role in stratifying a practice population so that only those at highest risk are offered diagnostic testing, rather than the whole population. This approach is likely to generate fewer anxiety-provoking false-positive results than population screening by questionnaire or urine test, as well as fewer costs, particularly if the score is automatically calculated by a practice computer. The benefits, costs, feasibility, and acceptance of such an approach in primary care are currently undergoing evaluation in a randomized clinical trial (29). This trial will also address the broader, unresolved question of whether the benefits of screening outweigh the costs (30).

The risk score performed well even in the absence of data on the variables that are less likely to be routinely recorded in general practice records, such as family history, with AUCs of 68.9–75.2%. Variables such as BMI and age contributed more to the predictive models than did, for example, family history. This suggests that the risk score may have utility in general practice, where some routine clinical information may be unavailable. Furthermore, BMI can be reliably calculated from self-reported height and weight when data are incomplete (31,32).

Limitations of the study
There were some minor differences between the methods of data collection for development and testing of the risk score and those used in the EPIC population. For example, clinical records of prescribed medications were used in the Wessex study rather than the self-reports used in the EPIC. Such a discrepancy is likely to have led to an underestimation of the performance of the risk score. Also, both the original Ely sample and the EPIC population were mostly Caucasian. Ethnic differences are known to affect the prevalence of type 2 diabetes, prevalence of risk factors, and the extent to which undiagnosed diabetes is associated with various risk factors (33–35). Consequently, the performance of the risk score and other similar methods may be different in areas with greater ethnic diversity; these methods should be tested in such populations.

In conclusion, a simple risk score incorporating data routinely collected in general practice is effective in detecting individuals at high risk of having undiagnosed hyperglycemia, as defined by elevated GHb, in a large and representative population. Such a score could form part of a strategy for reducing the current delay between development and recognition of type 2 diabetes and an alternative to either testing all those over age 45 years, as is recommended by the American Diabetes Association (7), or distributing and analyzing risk factor questionnaires.

APPENDIX — The logistic model predicting risk of prevalent diabetes (10) is defined as

$$\text{Probability of having type 2 diabetes} = \frac{1}{1 + e^{-\alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n}}$$

where $\alpha = -6.322$, $\beta_1 x_1 = -0.879$ ($x_1 = 1$ if female, 0 if male); $\beta_2 x_2 = 1.222$ ($x_2 = 1$ if prescribed antihypertensive medication, 0 if not); $\beta_3 x_3 = 2.191$ ($x_3 = 1$ if prescribed steroids, 0 if not); $\beta_4 x_4 = 0.063$ ($x_4$ is age in years); $\beta_5 x_5 = 0$ if BMI $< 25$, 0.699 if BMI $\geq 25$ and $< 27.5$, 1.97 if BMI $\geq 27.5$ and $< 30$, and 2.518 if BMI $\geq 30$; $\beta_6 x_6 = 0$ if the person has no first degree relative with diabetes, 0.728 if there is a parent or sibling with diabetes, or 0.753 if there is both a parent and sibling with diabetes; $\beta_7 x_7 = 0$ for non-smokers, −0.218 for ex-smokers, and 0.855 for current smokers.

Figure 2 — The ROC curves for the risk score and PM1 in the EPIC-Norfolk population.
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