ORIGINAL RESEARCH

The development and validation of the Portuguese risk score for detecting type 2 diabetes and impaired fasting glucose

Laura J. Gray, Henrique Barros, Luis Raposo, Kamlesh Khunti, Melanie J. Davies, Ana Cristina Santos

Aims: To develop and validate a non-invasive score for detecting undiagnosed impaired fasting glucose (IFG) and type 2 diabetes (T2DM) in a Portuguese population.

Methods: We used data from 3,374 individuals aged 18–94 years from a Portuguese cross-sectional study. We developed a logistic regression model for predicting IFG/T2DM (diagnosed using fasting glucose). We externally validated the score using data from two cohorts of the EPI-Porto study, cross-sectional (n = 2,131) and data from the 5 year follow-up (n = 1,304).

Results: The final model included age, sex, BMI and hypertension with an area under the ROC curve of 70.1 (95%CI 68.4, 71.7). Using a cut-point which classifies 50% of the EPI-Porto cross-sectional data as high-risk gave sensitivity 73.2% (95%CI 68.5%, 77.6%), specificity 55.5% (53.1%, 57.8%), positive predictive value (PPV) 27.0% (24.3%, 29.8%) and negative predictive value (NPV) 90.2% (88.3%, 92.0%) for IFG/T2DM. Using the same cut-point on the prospective data classified 45% as high-risk; sensitivity 69.1% (63.4%, 74.4%), specificity 63.3% (60.0%, 66.5%), PPV 38.0% (33.9%, 42.4%), and NPV 86.2% (83.3%, 88.8%).

Conclusion: The Portuguese risk score can be used to identify those at high risk of both prevalent undiagnosed and incident IFG/T2DM.

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1. Introduction

Type 2 diabetes (T2DM) is a growing world-wide problem. It is estimated that 366 million people world-wide have diabetes raising to 522 million by 2030 [1] and that the death rates attributable to diabetes will double between 2005 and 2030 [2]. T2DM is usually preceded by the ‘pre-diabetic’ state called impaired glucose regulation (IGR), which includes impaired fasting glucose (IFG) and impaired glucose tolerance.

Abbreviations: IGR, impaired glucose regulation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; ROC, receiver operator characteristic; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratios for a positive test; LR−, likelihood ratios for a negative test.

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(IGT). T2DM and IGR are associated with increased risk of cardiovascular disease [3,4]. Both IGR and T2DM are often asymptomatic, many cases remain undiagnosed and therefore, untreated. The International Diabetes Federation estimates that there are 183 million cases of undiagnosed diabetes world-wide [1].

The PREVIDIAB study was the first population based diabetes prevalence study carried out in Portugal. The study reported a prevalence of diabetes of 11.7%, with 5.1% being previously undiagnosed [5]. The rates of IGR were much higher at 23.3% (10.6% IFG); this demonstrates a large population at risk of T2DM. Randomised controlled trials have shown that progression from IGT to diabetes can be prevented through lifestyle modification and that this is likely to be cost effective [6,7]. Although data regarding prevention in those with IGR is lacking, many bodies around the world are now recommending measuring fasting blood glucose alone as it is much less resource intensive than a full oral glucose tolerance test [8,9]. Additionally utilising a low cut point for IFG (5.6 mmol/l versus 6.0 mmol/l) has also been shown to have a high level of sensitivity (82%) for detecting IGT [10]. Early detection of those with elevated glucose levels gives a window of opportunity for the prevention of T2DM and the reduction of potential micro and macro-vascular complications.

Population based screening offers an opportunity for early case detection, but is expensive and impractical. Targeted screening to high risk groups has been shown to be more efficient, and results in a higher positive diagnostic yield than testing the whole population [11–13]. One method of risk stratifying a population is the use of risk scores. Self-assessment scores are simple questionnaire based risk scores which allow members of the public to calculate and interpret their own risk of disease. Many self-assessment risk scores have been developed world-wide [14–16], but validation studies show that scores developed for a particular population often do not perform well when used elsewhere [15].

The aim of this study was to develop and validate a simple score which can be completed by a lay person for detecting previously undiagnosed IFG and T2DM for use in a Portuguese population.

2. Methods

2.1. Development data set

The data used to develop the risk score was taken from the PORMETS cross-sectional study which was designed to establish the prevalence of the metabolic syndrome in mainland Portugal [17]. Two primary health care centres from each of the 18 Portuguese mainland districts were included, one from the district’s capital and another representative of the non-urban area (apart from Setubal where only one centre was included). In each centre 120 participants were selected at random for inclusion. A total of 4,105 participants were included between February 2007 and July 2009. A structured questionnaire was given to each participant, collecting information on personal medical history, socio-demographic and behavioural characteristics.

Participants were considered current smokers if they smoked daily or occasionally and an ex-smoker if they had stopped smoking for at least 6 months. Regarding alcohol intake, participants were categorised as an occasional drinker if they had less than a drink per day, a daily drinker if they have at least a drink per day and non-drinker if they did not consume any type of alcoholic beverages. Participants were categorised as engaging in regular physical exercise if they took part in a leisure time physical activity preformed on a repeated basis, spending at least 30 min a week.

Anthropometric measures were taken, namely weight, height, and waist circumferences. Body weight was measured to the nearest 0.1 kg using a digital scale, and height to the nearest centimetre in the standing position using a wall stadiometer. Waist circumference was measured midway between the lower limit of the rib cage and the iliac crest. A fasting venous blood sample was collected by trained nurse. Participants were classified as having IFG if their fasting glucose was ≥5.6 mmol/l and T2DM was defined as a fasting glucose result of ≥7.0 mmol/l [9].

Those with previously diagnosed diabetes or having reported taking anti diabetic medication or insulin were excluded from the development data set. We also excluded those without a fasting glucose measurement.

2.2. Variables considered

Only variables which can be self-completed by a lay person without intervention from a health care professional or the results of medical tests were considered for inclusion. These variables included age, sex, medical history of stroke or myocardial infarction, level of physical activity, waist circumference, statin therapy, current hypertension, BMI and current smoking status. The development data set has 388 events (IGF or T2DM), which gives around 38 events per variable being assessed which is above the general rule of thumb of 10 to 20 events per variable [18]; hence the sample size is adequate for this analysis. The pool of potential variables assessed covers the majority of those included in previously developed screening tools, although data on family history of diabetes were not recorded [3,14].

2.3. Modelling

All modelling was carried out in Stata (version 10) using logistic regression with a composite of screen detected IFG/T2DM as the dependent variable. A non-automated approach was taken for variable selection; initially each variable was modelled to see if it independently predicted the outcome. Sets of predictors shown to be independently related were then considered. At each step the area under the receiver operator characteristic (ROC) curve was used to compare models in addition to the p value for the covariate of interest (with significance levels set at p ≥ 0.05). All measured variables were initially considered for inclusion in their original continuous form. Once a final model was chosen we then tested various categorisations to see which best fitted the data. Although collapsing continuous variables into groups is not best practice, this score is to be completed by hand by the public and
therefore needs to be as simple as possible. To keep the score simple we did not consider interaction terms.

2.4. Missing data

The level of missing covariate data varied but was minimal for the majority of variables (ranging from 0.1% for current hypertension to 1.7% for smoking status), apart from statin use (36%). The effect of missing data on both the modelling process and the final model chosen was assessed using the multiple imputation command MI in Stata [19]. MI replaces missing values with multiple sets of simulated values to complete the data, performs standard analysis on each completed dataset, and adjusts the obtained parameter estimates for missing-data uncertainty using Rubin’s rules to combine estimates.

2.5. Creating a score

To derive the scores allocated to each element of the final model the ß coefficients were multiplied by 10 and rounded up to the nearest integer. The total score is then calculated by summing across these. This method had been used in several other scoring systems [20–22]. The discrimination of the score was assessed using the area under the ROC curve. Calibration was assessed using the Hosmer–Lemeshow statistic [23].

2.6. External validation

The final score was validated using two external data sets. Both data sets come from the EPI-Porto study, a detailed description of the study has been published previously [24]. Briefly, non-institutionalised inhabitants of Porto, Portugal, were selected using random digit dialling. After identification of a household, permanent adult residents were characterised according to age and gender, and one adult was selected by simple random sampling and invited to take part in the study. Participants completed an interview based on a structured questionnaire. Data on social, demographic, past personal and family medical conditions, medication and behavioural characteristics (regarding smoking; participants who smoked during the previous 12 months were classified as smokers) were self-reported. Anthropometric data were obtained after a 12-h fast using methods comparable to the PORMETS study. All participants were invited back for follow up at 5 years, 67.6% of those invited attended [25]. The baseline data collection was repeated.

The Portugal risk score was validated using the cross-sectional baseline data to establish the discriminative ability of the score for prevalent screen-detected disease, those with previously diagnosed diabetes or missing fasting glucose measures were excluded. The score was also validated using the prospective data to assess if score could also be used to assess future risk of developing IFG/T2DM. This cohort was limited to only those who attended follow-up, as before those with previously diagnosed diabetes or missing glucose measures were excluded along with those who were found to have either diabetes or IFG at the baseline assessment. A sensitivity analysis was carried out including those with IFG at baseline in the T2DM alone analysis.

The validity of scores was assessed using the area under the ROC curve. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and likelihood ratios for a positive test (LR+) and a negative test (LR−) with 95% confidence intervals, comparing each cut point on the score to the fasting glucose result (reference standard), were also calculated. These were calculated for both the composite of IFG/T2DM and for T2DM alone.

3. Results

The characteristics of the development data and the external validation cohorts are shown in Table 1. 3,374 participants without previous diabetes and with fasting glucose measured were included from the PORMETS study. The mean age was 51.5 years, with 41% male; 2,131 were included from the EPI-Porto cross-sectional cohort and 1,304 from the prospective cohort. The PORMETS study data and the EPI-Porto cross-sectional data were broadly similar; the EPI-Porto data had less males with slightly lower body weight and slightly higher blood pressure, cholesterol and fasting glucose. The prospective data were comparable to the cross-sectional data. In terms of outcomes equivalent levels of screen-detected T2DM were seen in both PORMETS and EPI-Porto at baseline, with a higher percentage at follow up of the EPI-Porto study. 16.7% of the EPI-Porto participants had IFG at baseline increasing to 22.8% at follow up compared to 11.5% in the PORMETS study.

3.1. Score development

Table 2 shows the final model and the scoring system. The following variables were found to be predictive of screen-detected IFG/T2DM: age, sex, BMI and current hypertension. The final model had an area under the ROC curve of 0.74 (95% CI 0.72, 0.77), with acceptable agreement between the observed and predicted estimates (Hosmer–Lemeshow test: χ² = 13.0, p = 0.11). Age and BMI were both collapsed into categorical variables; the re-parameterisation of these variables did not affect the overall fit of the model. The final scoring system ranges from 0 to 39 with a higher score reflecting greater risk.

We used multiple imputation to estimate the effect of missing data on both the final model produced and the scores allocated to each variable included. Based on the imputed datasets the same predictors would be included in the final model and the scoring of those predictors would remain unchanged.

3.2. External validation – cross-sectional data

Table 3 shows the external validation of the Portugal risk score using the EPI-Porto cross-sectional data for both IFG/T2DM and T2DM alone. Fig. 1 (i) and (ii) shows the ROC curves. Using a cut point of greater than or equal to 23 defines 50% of the population at high-risk (currently recommended by the National Institute for Clinical Excellence in the UK [8]), this picks up 73% of those with IFG/T2DM and of those screened 27% will have IFG/T2DM. The same cut point picks up 82% of those with T2DM. 3% of those screened will have T2DM alone. Screening
Table 1 – Characteristics of the data used to develop and validate the score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PORMETS development cross-sectional</th>
<th>EPI-Porto validation cross-sectional</th>
<th>EPI-Porto validation prospective – baseline</th>
<th>EPI-Porto validation prospective – follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number included</td>
<td>3374</td>
<td>2131</td>
<td>1304</td>
<td>1304</td>
</tr>
<tr>
<td>Years to follow up, mean (SD)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.1 (2.5)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>51.5 (16.5)</td>
<td>51.7 (15.4)</td>
<td>50.9 (14.8)</td>
<td>55.6 (15.3)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>1385 (41.1)</td>
<td>813 (38.2)</td>
<td>455 (34.9)</td>
<td>455 (34.9)</td>
</tr>
<tr>
<td>Weight, mean (SD)</td>
<td>71.4 (13.6)</td>
<td>68.7 (13.0)</td>
<td>67.9 (12.6)</td>
<td>68.4 (13.1)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.0 (4.6)</td>
<td>26.6 (4.6)</td>
<td>26.3 (4.5)</td>
<td>26.7 (4.7)</td>
</tr>
<tr>
<td>Waist circumference, mean (SD)</td>
<td>92.3 (12.2)</td>
<td>88.0 (12.4)</td>
<td>86.7 (12.1)</td>
<td>90.4 (12.1)</td>
</tr>
<tr>
<td>Systolic BP, mean (SD)</td>
<td>130.3 (22.1)</td>
<td>134.0 (22.9)</td>
<td>132.0 (22.5)</td>
<td>128.9 (21.1)</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD)</td>
<td>78.1 (12.3)</td>
<td>82.3 (11.7)</td>
<td>81.6 (11.5)</td>
<td>79.8 (11.3)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>520 (15.7)</td>
<td>533 (25.4)</td>
<td>316 (24.5)</td>
<td>–</td>
</tr>
<tr>
<td>Physical activitya, n (%)</td>
<td>916 (27.5)</td>
<td>849 (35.0)</td>
<td>493 (38.2)</td>
<td>–</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD)</td>
<td>5.4 (1.1)</td>
<td>5.6 (1.2)</td>
<td>5.6 (1.1)</td>
<td>5.5 (1.0)</td>
</tr>
<tr>
<td>HDL, mean (SD)</td>
<td>1.3 (0.3)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>Fasting glucose, mean (SD)</td>
<td>4.7 (0.9)</td>
<td>5.0 (0.9)</td>
<td>4.8 (0.5)</td>
<td>5.2 (0.8)</td>
</tr>
<tr>
<td>Antihypertensive therapy, n (%)</td>
<td>642 (29.7)</td>
<td>477 (22.4)</td>
<td>257 (19.7)</td>
<td>372 (29.3)</td>
</tr>
<tr>
<td>Statin therapy, n (%)</td>
<td>512 (23.7)</td>
<td>217 (8.7)</td>
<td>91 (7.0)</td>
<td>233 (18.3)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>82 (2.5)</td>
<td>61 (2.5)</td>
<td>15 (1.2)</td>
<td>–</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>118 (3.5)</td>
<td>65 (2.6)</td>
<td>22 (1.7)</td>
<td>–</td>
</tr>
<tr>
<td>Family history diabetes, n (%)</td>
<td>–</td>
<td>519 (24.4)</td>
<td>306 (23.5)</td>
<td>306 (23.5)</td>
</tr>
<tr>
<td>IFG, n (%)</td>
<td>338 (11.5)</td>
<td>356 (16.7)</td>
<td>0 (0)b</td>
<td>290 (22.8)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>50 (1.5)</td>
<td>35 (1.6)</td>
<td>0 (0)b</td>
<td>39 (3.0)</td>
</tr>
</tbody>
</table>

a Leisure time physical activity performed on a repeated basis, spending at least 30 min a week.
b Those diagnosed with type 2 diabetes or IFG at baseline were excluded from the prospective data set.

3.3. External validation – prospective data

The score also works well on the prospective data set (see Table 3, Fig. 1(iii) and (iv)). Using the same cut point of 23, 45% of the population would be invited for further testing. This gives a sensitivity of 69% and a specificity of 63% for IFG/T2DM and 75% and 56% for T2DM alone. Across all cut points for both the cross-sectional and prospective data high negative predictive values are seen, suggesting that those who have a low score had a high rate of being true negatives. Including those with IFG at baseline for T2DM alone slightly increases the number screened for each cut point and also the detection rates.

4. Discussion

We have developed a simple and sensitive self-assessment screening tool for use in a Portuguese population that can be
The oral glucose tolerance test is known to be a cost-effective [8], and in some cases, a cost-saving example the UK [8], and modelling studies have found this targeted screening is recommended in some countries, for this early identification did not improve outcomes [28]. The brought forward diagnosis by an average 3.3 years but that [27]. Another UK study found that screening for diabetes approached rather than population-based approach increased in those screening programmes taking a multi-step study also found that attendance rates to screening were following screen-detection of T2DM, but to date there have found a small non-significant benefit in terms of reducing the incidence of CVD and death in those intensively treated. This was the first study to look at hard outcomes ing the incidence of CVD and death in those intensively treated. This was the first study to look at hard outcomes

### Table 3 – External validation of the risk score using both the Porto cross-sectional data and the prospective data.

<table>
<thead>
<tr>
<th>Cut point</th>
<th>Screened (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
</table>

#### Cross-sectional validation

| T2 diabetes/impaired fasting glucose | 58 | 82.1 (77.9, 85.8) | 47.8 (45.4, 50.2) | 26.1 (23.6, 28.6) | 92.2 (80.3, 93.9) | 1.57 (1.47, 1.68) | 0.38 (0.30, 0.47) |
| T2 diabetes alone | 21 | 58 | 90.9 (75.7, 98.1) | 42.8 (40.7, 45.0) | 2.5 (1.7, 3.5) | 99.7 (99.0, 99.9) | 1.59 (1.42, 1.78) | 0.21 (0.07, 0.63) |
| T2 diabetes with/without IGR at baseline included | 21 | 58 | 82.1 (77.9, 85.8) | 47.8 (45.4, 50.2) | 26.1 (23.6, 28.6) | 92.2 (80.3, 93.9) | 1.57 (1.47, 1.68) | 0.38 (0.30, 0.47) |

#### Prospective validation

| Type 2 diabetes/impaired fasting glucose | 53 | 77.8 (72.5, 82.4) | 55.7 (52.3, 59.0) | 36.4 (32.6, 40.4) | 88.5 (85.5, 91.0) | 1.75 (1.59, 1.93) | 0.40 (0.32, 0.50) |
| Type 2 diabetes only | 23 | 53 | 87.5 (71.0, 96.5) | 48.2 (45.3, 51.2) | 4.4 (3.0, 6.3) | 99.3 (98.2, 99.8) | 1.69 (1.47, 1.95) | 0.26 (0.10, 0.65) |
| Type 2 diabetes only with IGF at baseline included | 21 | 58 | 86.3 (72.6, 92.3) | 43.8 (41.2, 46.5) | 7.6 (5.9, 9.6) | 98.4 (97.0, 99.2) | 1.54 (1.39, 1.70) | 0.31 (0.18, 0.56) |
then continuous predictors could be included. Secondly, both the PORMETS study and the EPI-Porto study only measured fasting glucose on a single occasion and did not perform a full oral glucose tolerance test or measure HbA1c. HbA1c is now recommended for the diagnosis of T2DM by WHO but not IGR [34]. Using HbA1c to diagnose T2DM significantly increases the number diagnosed and these are generally of a lower risk phenotype [35]. When HbA1c was included in the outcome for the Leicester Practice Score similar variables to scores not including HbA1c were included [36]. Future work should aim to validate this score using data from both the oral glucose tolerance test and HbA1c. Thirdly, the PORMETS study did not collect data on family history of diabetes. Family history of diabetes is a known risk factor for T2DM [37] and has been included in many previously developed risk scores [14]. Although its inclusion may improve the predictive ability of the score, the levels of sensitivity and specificity seen are in line with other scores which include family history [20,36].

This study also has a number of strengths. The sample size used to develop the score (n = 3,374) gave around 38 events per variable for the regression modelling. This is above the 10–20 events per variable recommended for this type of analysis and therefore limits the problem of over-fitting [38]. The PORMETS study had variable levels of missing data which could have affected the final model produced and the scores allocated to each variable within that model. We tested both of these scenarios using multiple imputation methods which showed that the final model produced and the scores were not affected by the level of missing data. Many previously developed scores have not assessed the impact of missing data [14].

In conclusion, we have developed a simple self-assessment risk score for detecting the risk of current undiagnosed IFG/T2DM in Portuguese adults. This score could be used to increase uptake to screening programmes and awareness of diabetes and its associated risks within this population. Future research should try and assess both the efficacy and cost-effectiveness in using this tool in a real-life setting to prevent diabetes and its complications.
Role of the funding source

Funding for an academic visit to the University of Porto was given by Santander. PROMETS study was funded by the Portuguese Society of Endocrinology, Diabetes and Metabolism and Bayer Health Care. EPi-Porto study was funded by Fundação para a Ciência e Tecnologia, POCTI/ESP/35767/99, POCTI/ESP/42361/2001, POCI/SAU-ESP/61160/2004. The funders had no role in the design or analysis of this study.

Contribution statement

LJG: substantial contribution to conception and design, analysis and interpretation of data; drafted the article; final approval of the version to be published. HB: substantial contribution to acquisition of data, revised article; final approval of the version to be published. LR: substantial contribution to acquisition of data, revised article; final approval of the version to be published. KK: substantial contribution to conception; revised article; final approval of the version to be published. MJD: substantial contribution to conception; revised article; final approval of the version to be published. ACS: substantial contribution to conception; revised article; final approval of the version to be published. LJG is guarantor of the paper.

Conflicts of interest

KK (Chair), and MJD are members of the National Institute for Health and Clinical Excellence Public Health Guidance on prevention of Type 2 diabetes among people with prediabetes. MJD and KK are advisors to the UK Department Health for the NHS Health Checks Programme. MJD has received funds for research, honoraria for speaking at meetings and has served on Advisory Boards for Lilly, Sanofi Aventis, MSD, Novo Nordisk, BMS, BI and Roche. KK has received funds for research, honoraria for speaking at meetings and or served on Advisory Boards for Astra Zeneca, GSK, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis. All other authors have no conflicts of interest to declare.

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