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## Screening for diabetes.

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The United Kingdom National Screening Committee provides criteria against which screening programs can be evaluated: (<http://www.nsc.nhs.uk/pdfs/criteria.pdf>). Using these criteria, screening for diabetes in the general population was deemed not to be warranted in 2001 (1) as:

- 1/ the benefits of early diagnosis and treatment had not been proved
- 2/ screening for diabetes to reduce cardiovascular disease had not been shown to be effective
- 3/ disadvantages of screening were not quantified
- 4/ the clinical management of those with diabetes should be optimised before instituting a screening program

A more recent 2007 report on "Screening for type 2 diabetes" from the UK concluded that the case for screening was somewhat stronger, given the possible "options for reduction of cardiovascular disease" (mainly with statins) and "because of the rising prevalence of obesity and hence diabetes" (2). Further, since the 2001 evaluation, some of the possible disadvantages of screening have been quantified and found not to be of great harm (3-5).

In this issue of Diabetes Care, a Diabetes Risk Calculator is proposed, which aims to detect both undiagnosed diabetes as well as individuals with *either* undiagnosed diabetes or "pre-diabetes" (6). A number of other screening tools have already been developed in various populations, and are reviewed in the UK report (2). In particular, for the United States, Herman et al. developed a simple questionnaire based on NHANES II data (7), using a classification tree approach. The questionnaire included age, weight for height, exercise, diabetes in the family and delivery of a large baby. It is currently proposed by the American Diabetes Association as a "Diabetes Risk Test", <http://www.diabetes.org/risk-test.jsp>.

The Diabetes Risk Calculator (6) was developed and validated on American data, from NHANES III (1988-94): 7000 men and women aged  $\geq 20$  years. Diabetes and pre-diabetes were defined by a fasting plasma glucose and additionally for about half of the participants aged 40-75 years, the 2 hour glucose concentrations following an oral glucose tolerance test (OGTT) were also used. Thus the glucose phenotype identified by the tool is not homogeneous. A total of 18 potential explanatory variables were reviewed, all of which would be known to an individual. Two methods were compared for the development of a Calculator: logistic regression and Classification and Regression Tree (CART) analysis. Details are presented in a Technical Report available on line, prepared for GlaxoSmithKline.

For logistic regression, two methods of variable selection were used to detect "diabetes + prediabetes"

- 1/ the best model with  $k$  variables and

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2/ forward stepwise selection.

Pragmatically, the same equation was also used for predicting undiagnosed diabetes alone, even though there appear to be differences in the variables that would be chosen to predict the two entities (gender is included for one but not the other). Threshold values were determined to achieve sensitivities of 80% - a better criterion than the usual "optimum" threshold which corresponds to maximizing (sensitivity + specificity). The corresponding positive predictive values are not given. Ethnicity was not included for technical reasons as SAS is not able to cope with a 4 class variable in "best" model logistic regressions, but the stepwise technique could still have been used. This important variable has been included in the CART classification and found to be a discriminator. The final logistic regression model included *8 variables*: age, gender, weight, height, waist-hip ratio, BMI, high blood pressure and familial diabetes. While all of these variables were statistically significant, it is probable that some of the highly correlated anthropometric variables could be deleted without loss to the capacity of the model to predict undiagnosed diabetes. Indeed, in the formulation of the CART model, neither BMI nor waist hip ratio were included as possible variables to enter the model.

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The final CART model required *10 variables*: age, gender, weight, height, waist, high blood pressure, familial diabetes, exercise, ethnicity, gestational diabetes. The areas under the ROC curve for the two techniques were similar, as seen in Figure 7 of the Technical Report.

The logistic model is quickly dismissed as the CART is said to be of "equivalent accuracy but greater ease of use". The two methods have not been compared on equal grounds, as different variables were used in developing the two techniques. Further, the two methods were compared essentially by the areas under the ROC curves, which were very similar. Other characteristics for the CART method are difficult to compare with those of the logistic regression as the thresholds have been set to have a sensitivity of 80%. As for the "ease of use", the results from both techniques need to be written as an additive score, to provide a simple pre-screening score.

As a clinical tool, I am not sure whether a busy physician would take the time to go through a chart to calculate the probability of a patient having diabetes or prediabetes. It needs to be put into a more useable format, as has been done for the Diabetes Risk Test (7). A diabetes risk calculator could be developed in an electronic format or as a web-based facility to pre-screen for undiagnosed diabetes or pre-diabetes. It might be a useful tool for patients who would like to estimate their risk of diabetes.

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One of the unmet criteria for screening given above is that we have no hard evidence that screening for diabetes reduces cardiovascular risk. One trial is underway: the ADDITION Study is a randomised clinical trial which aims to study whether systematic screening and subsequent cardiovascular risk reduction have benefits on morbidity and mortality (8). Over 3000 primary care patients were recruited in the UK, Denmark and The Netherlands, and we now await the results from this 5-year trial.

Diabetic individuals with an isolated 2-hr hyperglycaemia, following an oral charge of glucose, are not detected by a fasting hyperglycaemia, and they deserve special attention. They tend to be older and slimmer and more are women (9). While (obviously) the prevalence of diabetes is increased when these individuals are included, the current article does provide information on this group, and we are told that "the lack of OGT data for some participants did not materially affect the stability of the results". It would be very useful to have a pre-screening tool *only* for this group, as they are not routinely picked up. From Table 3 in the Technical Report, in the individuals aged 40-74 years with both fasting and 2 hour glucose available, 3.2% had diabetes screened on the basis of an isolated 2 hour hyperglycaemia: almost 1/3 of the people screened as diabetic. A similar remark can be made for the "diabetes + pre-diabetes" group, where 7% of the population would be missed, 1/7 of the 49% of the NHANES population is in this group. These percentages are not trivial.

Adiposity plays a large part in the presence of hyperglycaemia, and it is still a first simple criterion for entry into any diabetes screening process. Further, the choice of the marker of adiposity is not important: BMI, waist circumference and waist hip ratio have similar discriminating capabilities (10).

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