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Are diabetes risk scores useful for the prediction of cardiovascular diseases? Assessment of seven diabetes risk scores in the KORA S4/F4 cohort study☆

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ABSTRACT

Aim: To evaluate the utility of diabetes prediction models for CVD prediction as stated in two earlier studies.
Methods: 845 subjects from the population based German KORA (Cooperative Health Research in the Region of Augsburg) S4/F4 cohort study (aged 55 to 74 years, without diabetes, former stroke, and former myocardial infarction at baseline) were followed for up to ten years for incident stroke and myocardial infarction. Seven diabetes risk scores developed from four different studies were applied to the KORA cohort to assess their predictive ability for CVD.
Results: Areas under the receiver-operating curve (AROCs) for the prediction of CVD ranged from 0.60 to 0.65 when diabetes risk scores were applied to the KORA cohort. When diabetes risk scores were used to predict CVD and type 2 diabetes, respectively, AROCs for the prediction of CVD were 0.09 to 0.24 lower than AROCs for the prediction of type 2 diabetes. Furthermore, we used KORA data to develop prediction models for either diabetes or CVD, and found that they differed widely in selected predictor variables.
Conclusion: In the older population, diabetes risk scores are not useful for the prediction of CVD, and prediction models for diabetes and CVD, respectively, require different parameters.

1. Introduction

Type 2 diabetes and cardiovascular disease (CVD) share several traditional risk factors like obesity, hypertension, and dyslipidaemia (Stern, 1995). Accordingly, the metabolic syndrome which is a cluster of these risk factors is associated with an increased risk of developing type 2 diabetes and CVD (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004; Meigs, 2004). Thus, one might assume that diabetes risk scores are also appropriate for the prediction of CVD. From focus groups with general practitioners in Germany, the authors concluded that the acceptance of risks scores might be larger if the scores offered the possibility of predicting several chronic diseases simultaneously (Müller-Riemenschneider et al., 2010). So far, the ability to predict CVD risk has been reported for two diabetes prediction models. The Finnish Diabetes Risk Score (FINDRISC) was used to predict the individual risk of coronary heart disease and stroke, and was considered to be a "reasonably good predictor" of these diseases (Silventoinen et al., 2005). However, the predictive ability of FINDRISC for coronary heart disease and stroke was considerably worse than for diabetes in the same middle-aged population (Lindström & Tuomilehto, 2003; Silventoinen et al., 2005). As CVD risk was assessed in the same surveys which were used to develop FINDRISC, it is difficult to state to what extent the worse CVD prediction can be attributed to a worse CVD predictive ability per se or to the fact that CVD prediction was assessed in the same surveys used to develop the diabetes score. Based on the German Diabetes Risk Score (GDRS), it was shown that subjects with an estimated diabetes risk of 5% to 10%, and of ≥ 10%, respectively, had a strongly increased risk of myocardial infarction, stroke, and cardiovascular mortality compared to subjects with a diabetes risk of < 1% (Heidemann et al., 2009). However, the authors did not investigate whether individual values of the score were useful to predict the risk of developing CVD, and no AROC values were presented.

For the present study, we selected seven diabetes risk scores (three KORA models (Rathmann et al., 2010), Framingham (Wilson et al., 2007), DESIR (Balkau et al., 2008), ARIC-1 (Kahn, Cheng,

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Thompson, Imperatore, & Gregg, 2009), ARIC-2 (Kahn et al., 2009)). Using the data of the KORA S4/F4 cohort study of older participants, our aim was to investigate (a) whether quartiles of diabetes risk scores are associated with individual cardiovascular risk, (b) whether individual diabetes risk estimates are suitable for prediction of CVD, (c) whether risk scores developed to predict CVD differ in included risk factors from risk scores developed to predict diabetes, and (d) whether it is possible to develop one risk score for both outcomes which predicts both endpoints at a clinically significant level.

2. Subjects, Materials and Methods

2.1. Study population

In the population-based KORA survey S4, carried out in 1999–2001, 2656 participants aged 55–74 years were invited for baseline investigations. Overall, 1653 (62%) subjects participated. Of these, 1353 subjects had a standard oral glucose tolerance test (OGTT) at baseline after excluding participants with known diabetes and further drop-outs, which were mainly subjects who were not able to attend an investigation during the morning hours (for details cf. (Rathmann et al., 2003)). Of the 1223 participants who were free of known or newly diagnosed diabetes at baseline, 68 were excluded because they had a former myocardial infarction (MI) or stroke at baseline.

The study group consisted of 845 subjects free of diabetes, MI and stroke at baseline, and with complete data of the KORA F4 follow-up for incident diabetes, incident MI and stroke. To maximize power for the CVD events, we have used the latest available follow-up which was ten years. For the diabetes events, we used the 7-year follow-up because results of oral glucose tolerance tests were not available for 10 years.

For supplementary analyses, data of a larger data set were used (1042 subjects without diabetes, MI and stroke at baseline, and with follow-up data for MI and stroke, regardless of availability of data for diabetes incidence). Contrary to the study group of 845 subjects, this larger study group includes also subjects without follow-up data for incident diabetes. Thus, the study group of 845 subjects used for the main analyses is a subgroup of the study group of 1042 subjects.

The survey was approved by the ethics committee of the Bavarian Medical Association.

2.2. Ascertainment of CVD

CVD was defined as stroke, myocardial infarction, or both. In detail, this included incidence of nonfatal or fatal myocardial infarction including sudden cardiac death and incidence of nonfatal or fatal stroke (ischemic or hemorrhagic). Mortality was ascertained by regularly checking the vital status of all sampled persons of the survey through the population registries inside and outside the study area. Death certificates were obtained from local health departments and coded for the underlying cause of death. Myocardial infarctions were identified through the population-based MONICA/KORA Myocardial Infarction Registry, which monitors the occurrence of all in- and out-of-hospital fatal and nonfatal myocardial infarctions among the 25 to 74-year-old inhabitants of the study region (Loewel, Lewis, Hoermann, & Keil, 1991). All incident cases of myocardial infarction above the age of 75 years or among persons not living in the study region as well as all incident cases of stroke were identified by self-report collected within the framework of follow-up questionnaires, which were sent to the still alive participants on a regular basis. Initially identified self-reported incident cases and the self-reported date of diagnosis were validated by hospital records or by contacting the probands treating doctor. Furthermore, the hospital records of those deceased during the follow-up period without a diagnosis of myocardial infarction (for persons aged 75 years and older or persons not living in the study region) or stroke at baseline were also examined and/or their last treating doctors were contacted. The records were searched for or the doctors were asked for a history of myocardial infarction or stroke and if a person had suffered from one of these diagnoses, the date of diagnosis was ascertained.

2.3. Ascertainment of diabetes and prediabetes

In the KORA surveys, self-reported diabetes cases were validated by contacting the general practitioners who treated the participants. At baseline and at follow-up, OGTTs were performed during the morning hours (range 7:00 to 11:00 h) for subjects without previously known diabetes. Participants were asked to fast for at least 10 h overnight, to avoid heavy physical activity on the day before examination, and to refrain from smoking before and during the test. Exclusion criteria for the OGTT were acute illnesses (infection, fever, acute gastrointestinal diseases). Fasting venous blood glucose was sampled and 75 g of anhydrous glucose was given (Dextro OGT, Boehringer Mannheim).

Prevalent diabetes and incident diabetes were defined based on (i) validated physician diagnoses, or (ii) newly diagnosed diabetes ($\geq$7.0 mmol/l fasting or $\geq$ 11.1 mmol/l 2 h post glucose load, OGTT). Prediabetes comprised impaired fasting glucose, impaired glucose tolerance, or a combination of both according to the 1999 WHO diagnostic criteria (World Health Organisation, 1999).

2.4. Physical examinations and interviews

Height, weight, waist circumference, systolic and diastolic blood pressure were measured based on standard protocols as described elsewhere (Rathmann et al., 2003). Trained medical interviewers gathered information on sociodemographic variables, physical activity, alcohol consumption, smoking, and parental history of diabetes.

2.5. Laboratory measurements

Blood was collected without stasis. All blood parameters except for 2-h glucose were based on fasting blood samples. After blood withdrawal the blood samples were centrifuged and kept cool (4 °C) until analyzing glucose in the central laboratory, which took place within a maximum of six hours after withdrawal. Blood glucose, HbA1c, HDL-cholesterol, triglycerides and serum uric acid were determined as described elsewhere (Rathmann et al., 2003).

2.6. Selection of diabetes risk scores

We selected seven diabetes risk scores which could be applied to KORA data without any modification (KORA models 1 to 3 (Rathmann et al., 2010), Framingham (Wilson et al., 2007), DESIR (Balkau et al., 2008), ARIC-1 (Kahn et al., 2009), ARIC-2 (Kahn et al., 2009)). The German Diabetes Risk Score (GDRS) (Heidemann et al., 2009) and the Finnish Diabetes Risk Score (FINDRISC) (Lindström & Tuomilehto, 2003) could not be taken into account because some variables included in these scores were not available in the KORA data set.

2.7. Statistical analyses

Cox proportional hazards models were fitted to calculate hazard ratios for incident CVD according to quartiles of estimated probabilities of developing diabetes (KORA models), or according to quartiles of point scores (Framingham, ARIC-1, ARIC-2). The DESIR model was not taken into account in this analysis because the small range of point scores did not allow a meaningful calculation of quartiles. Meeting the proportional hazard assumption was verified by including time-dependent covariables (interaction terms of the independent variable and survival time).