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Journal

The Lancet Diabetes & Endocrinology, 1(3)

ISSN

2213-8587

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Publication Date

2013-11-01

DOI

10.1016/s2213-8587(13)70048-2

Peer reviewed

HHS Public Access

Author manuscript

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2015 May 13.

Published in final edited form as:

Lancet Diabetes Endocrinol. 2013 November ; 1(3): 183–190. doi:10.1016/S2213-8587(13)70048-2.

Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study

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Abstract

Background—Patients with type 2 diabetes (T2DM) are twice as likely to develop dementia though it's difficult to predict who has the highest future risk. We created and validated a practical summary risk score providing an individualized estimate of the 10-year dementia risk in T2DM patients.

Methods—Two longitudinal cohorts T2DM patients aged 60 + with ten years follow-up were used to create (Diabetes and Aging Study N=29,961) and validate (Pathways Study N=2,413) the risk score. We built our prediction model by evaluating 45 candidate predictors using Cox proportional hazard models and developed a point system for the risk score based on the size of the predictor's beta coefficient. Model prediction was tested by discrimination and calibration methods. Dementia risk per sum score was calculated with Kaplan-Meier estimates.

Findings—Microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic events, depression, age and education most strongly predicted dementia and constitute the risk score (c-statistic= 0.73 creation cohort, c statistic =0.74 validation cohort). There was a 15-fold difference (5% vs. 73%) in observed dementia risk between the lowest (-1) and the highest (≥12) sum score.

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Contributors

LGE: participated in study design, conducted analyses, data collection, interpretation of data, drafting of the original manuscript and editing of final versions. GJB: concept of the DSDRS, participated in study design, project supervision, interpretation of data, and editing the manuscript. AJK: participated in study design, primary collection of data, review of manuscript drafts. ESH: participated in study design and critical review of manuscript drafts. WJK: participated in study design of the validation study, primary data collection of validation cohort, and review of manuscript. JRM: participated in study design, data interpretation, editing the manuscript. RAW: funding of the study, study supervision, access to the data, study design, oversight of analytic plan, data collection, data interpretation, and writing. RAW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

G J Biessels consults for and receives research support from Boehringer Ingelheim, and consults for Takeda Pharmaceuticals. The other authors have no conflict of interest to declare.

Interpretation—This is the first risk score capable of predicting 10-year individualized dementia risk in patients with T2DM. The risk score can be used to increase vigilance for cognitive deterioration and to selection of high risk patients for clinical trials.

Funding—NIH DK081796, Kaiser Permanente Community Benefit grant, Utrecht University high potential grant, VIDI grant 91711384 from ZonMw and Fulbright Fellowship.

Introduction

The rising prevalence of type 2 diabetes (T2DM) is of great public health concern, especially because diabetes can lead to complications in several organ systems. Over the last decades patients with T2DM are living longer due to major improvements in treatment and demographic trends.[1] This improved longevity is however accompanied by an increased risk of geriatric health complications, including cognitive impairment and dementia.[2] Adults with T2DM have approximately a two-fold greater risk of dementia, both Alzheimer's disease and vascular dementia, compared to adults without T2DM.[3]

Currently, there is no effective treatment to cure or prevent dementia, despite substantial efforts. In the recent years, attention has turned to early intervention strategies at a stage when there still is time and potential to modify disease progression.[4,5] Nevertheless, prevention trials have not yet shown the desired effect. To increase the chances of success of future trials, enrichment of study cohorts through risk stratification has been recommended.[4] A similar approach has been followed successfully in the cardiovascular field, where risk scores are used to select people for targeted treatment.[6,7] Recently, several risk scores to predict the risk of dementia have been published (see research in context panel).[8-11] However, none of these scoring systems account for diabetes-specific dementia predictors, such as diabetes duration, glucose lowering treatment, and severe hypoglycaemic episodes (see research in context panel).[12-15,15-18] Since people with T2DM are particularly vulnerable to dementia it is even more critical to identify those at high risk in early stages. The aim of this study was to develop and validate a risk score to predict the ten year individual dementia risk in older individuals with T2DM which can be easily implemented in daily clinical care.

Methods

Population

For the development of the risk score we evaluated 29,961 patients aged ≥60 years) with T2DM who were members of the Kaiser Permanente Northern California (KPNC) Diabetes Registry ("Registry"). This well characterized cohort of patients with diabetes has been the basis of several epidemiologic and health services studies[18-21] since 1994, as part of the Diabetes and Aging study. KPNC is a large, integrated health care delivery system providing comprehensive medical services to ~3·3 million members, representing ~30% of the surrounding population. Its membership closely approximates the general population by race/ethnicity and socioeconomic status with exception for slight underrepresentation of individuals in the extreme tails of income distribution.[22]

Analytic Cohort

The Registry identifies individuals with diabetes by a clinical algorithm based on electronic medical records: outpatient encounter files (diagnosis of diabetes); pharmacy prescriptions for diabetes medications; glycosylated hemoglobin (HbA1c) values greater than 7% in laboratory files; primary hospital discharge diagnoses of diabetes; and emergency room (ED) records of diabetes as the reason for visit; type of diabetes was determined using an algorithm based on self-reported clinical characteristics as well as inpatient and outpatient diagnoses.[19] The Registry has an estimated sensitivity of 99% based on chart review validation.[21] Between 1994-1997, all members of the Registry were mailed a survey to collect sociodemographic and health behaviours information (response rate 83%). Previously, we found no indication of bias from differences in characteristics or epidemiologic associations by survey respondent status.[20,23] Patients participating in the survey with T2DM formed our analytic cohort (N=62,616) . Further inclusion criteria were: i) alive at baseline (January 1, 1998); ii) no dementia diagnosis at baseline; iii) no gap of >3 months in health plan membership during the two years prior to baseline; and iv) age >60 years at baseline. The final cohort consisted of 29,961 patients.

Data Collection

Dementia Diagnoses—Dementia was identified between January 1,1998 and January 1, 2008 from electronic medical records using ICD-9-CM diagnosis codes of senile dementia uncomplicated , Alzheimer disease ,vascular dementia , and dementia not otherwise specified using initial diagnoses made in primary care (ICD 9 codes 290.0, 290.1x) and neurology or memory clinic visits (ICD 9 codes 331.0, 290.1x, 290.2x, 290.3, 290.4x). This ascertainment scheme has been used successfully in several recent studies of this population.[18] This strategy was found to have a sensitivity of 77% and specificity of 95% compared to a consensus diagnosis of dementia based on a neuropsychiatric battery, physical examination, structured interview with informants, and review of medical records.[15]

Candidate predictors—The candidate predictors were collected prior to baseline (January 1, 1998)(Table 1). Self-reported data extracted from the survey included: education, duration of diabetes, smoking status, alcohol use, weight, height, and race/ethnicity. Race/ethnicity included six categories (white, African American, Asian, Hispanic, Native American, or other).

Medication use was evaluated using a database of all outpatient prescriptions filled in KPNC pharmacies using an established protocol.[24] We defined a medication as dispensed if there was at least one fill for a prescription for a given medication, with at least a 30 days' supply in the 6 months prior to baseline(between June 1, 1997- January 1, 1998). Diabetes pharmacotherapy was classified as: insulin only, oral agent only (i.e. insulin secretagogues such as sulfonylureas or insulin sensitizers such as metformin and thiazolidinediones), insulin and oral agent combined, or no glucose lowering pharmacotherapy. Other extracted medications are: antiarrhythmics, digoxin, benzodiazepine, neuroleptics, antiseizure, antidepressants, antilipemics, diabetes-related and blood pressure medication use. For combination medications, we registered each distinct pharmacological agent. Two

physicians reviewed the list of prescribed medications to determine if they belonged to one of the medication groups (Drs. Huang and Exalto).

We used the aggregate of the most recent three HbA1c measurements reported in KPNC laboratory databases between January 1, 1996 and January 1, 1998.

Comorbid diseases were identified via hospitalization and outpatient records, based on established coding algorithms using primary diagnostic (ICD-9) or current procedural terminology (CPT) codes (Table 2). All comorbid diseases were identified between 1996-1998 except for cardiovascular disease, cerebrovascular disease, and head trauma for which we considered life-time prevalence based on hospitalization discharge data from 1979 till 1997.

Statistical Analysis and Modeling Strategy

Selection of predictors for the final risk score was based on three sequential steps. (Figure 1) Step 1: We identified 45 candidate predictors, based on previous epidemiological and etiological studies in the general population and/or in T2DM patients. These 45 candidate predictors were evaluated against three main criteria. Firstly, the prevalence of the predictor was ≥5 % in the dementia group with a dementia incidence rate >300 per 10,000 person years. The continuous variables had to be categorized for this step. We first assessed if the relation with dementia was linear, in models adjusted for age, gender education and ethnicity. Categorization was based on the outcomes of these models. Age, T2DM duration, age at T2DM diagnosis was categorized in 5 years strata. For HbA1c and BMI we used clinically established categories. In case of U-shaped relationships with dementia values representing the lowest risk were used as reference (see for example HbA1c in Table 1). Among the 45 candidate predictors, 18 met the prevalence and the incidence rate selection criteria. Candidate predictors not meeting the prevalence criteria, but with a markedly increased incidence rate, were merged into a single predictor (e.g. severe hypoglycemic and severe hyperglycemic events were merged into the predictor “acute metabolic events”). These merged predictors (n=6) were in some cases based on one or more of candidate predictors that already fulfilled the selection criteria (n=18). At the end of this first step, 16 mutually exclusive candidate predictors were selected for step 2 (Table 3).

Step 2: In the next step we assessed if the predictor was significantly associated with ten year dementia risk in Cox proportional hazard models, adjusted for age, gender, education, and race, taking into account censoring and time to dementia diagnosis. The selected candidate predictors were all significantly associated with dementia in Cox proportional hazards models adjusted for age, education, race, and gender (Table 3). Several of the predictors were likely to be interrelated (e.g. DM duration and DM treatment; digoxin use and cardiovascular disease). We therefore explored candidate predictors that were likely to be interrelated (based on existing knowledge from the literature) in multivariable models (e.g. all diabetes specific variables, all macrovascular conditions and all medications). The strongest independent predictors were selected from each group (data not shown). After this step the following candidate predictors were selected for step 3: age, education, hospitalization, acute metabolic event, depression, microvascular disease, cardiovascular disease, cerebrovascular disease.

Step 3: The remaining candidate predictors were evaluated in multivariable Cox proportional hazard models and the predictive ability was analyzed. The strongest candidate predictors (β coefficients comparable to 5-year of aging) were put together in one model (age, education, acute metabolic events, diabetic foot, depression and cerebrovascular disease). The other two candidate predictors (hospitalization and microvascular disease) were separately added. Based on predictive ability, the optimal final model was created. The model containing age, education, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, and depression most strongly predicted ten year dementia risk. The risk score was created by substituting the β coefficients of the final multivariable prediction model by points. The β coefficient of 5 years of age (continuous variable) was used as a reference standard and assigned two points. With this approach all variables with a (rounded) beta coefficient that was the equivalent of 2.5 years of ageing (i.e. 1 point) qualified for inclusion in the final model (Table 4).

The use of points rather than beta coefficients facilitates the practical use of the risk score. Previously published dementia risk scores also mostly used 5-year age categories (research in context panel in main manuscript). The β coefficients of gender and race were not large enough to assign points for the final model. Rerunning the final model with gender and race did not change the predictive ability.

Discrimination and calibration were used to assess the predictive accuracy of the models. Discrimination refers to the model's ability to distinguish between those who develop dementia and those who do not and was assessed taking into account survival using Harrell's c-statistic[25]. Calibration refers to the agreement between predicted and observed risk and was calculated with the Hosmer-Lemeshow chi square test.[25] Well-fitted models show non-significance on the Hosmer-Lemeshow chi square, indicating that modelled and observed prediction are not significantly different.

The risk score was created by substituting the β coefficients of the final prediction model by points. The β coefficient of 5 years of age (continuous variable) was used as a reference standard and assigned two points. Kaplan Meier estimates were used to calculate the observed ten year dementia risk per sum score. In addition, the average time to incident dementia per sum score was calculated. Lastly, a Cox proportional hazards model with the sum score as the only variable was fitted to compare the increase in risk by each level of the sum score. As a post-hoc analysis, the distribution of observed dementia risk per sum score within 5-year age categories was evaluated with Kaplan Meier estimates.

All analyses were performed using SAS version 9·1 (SAS Institute, Cary, NC), and associations were considered statistically significant at the 0·05 level.

External Validation

For external validation, we used a cohort of 2,413 older (age ≥60 years) patients with T2DM who are members of the Pathways Epidemiologic Study of Group Health (GH) from Washington State.[15,26] GH is a mixed model capitated health plan serving over 500.000 members in Washington State. Most members receive health care within the integrated health practice, which includes approximately 30 primary care clinics in Western

Washington State. GH enrollment is demographically similar to the area population with the exception of fewer persons in the highest income range. The GH diabetes registry identifies individuals with diabetes by a clinical algorithm. For the Pathways Study 4,839 patients (61·7% of the eligible patients) returned the baseline mail questionnaire, providing sociodemographics and health behaviors information. Approval to review medical records was received from 4,128 of these patients.

Patients were selected for the Group Health (GH) diabetes registry (between 2000 and 2002) based on meeting any of the following eligibility criteria in the prior 12 months: two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, a prescription for insulin or an oral hypoglycemic agent, two outpatient diagnoses or any inpatient diagnosis of diabetes.

For the validation cohort the same inclusion criteria were used as for the development cohort. Excluded were i) patients under 60 years of age (N=1,622), ii) Type 1 diabetes (N=184), or iii) who had dementia at baseline (N=76). The final cohort consisted of 2,413 patients. Data collection and definitions of all variables (including dementia outcome) were identical to the KPNC cohort, with the exception of end-stage renal disease (Table 2) and the study start date, baseline is between Mar 1, 2001-Sep 1, 2001. There is a 10 year follow-up for dementia diagnoses. Comorbid diseases were identified 6 months prior to the individual inclusion at baseline. The validation of the risk score was performed by fitting a Cox proportional hazards model with the sum score as the only predictor. Predictive accuracy in the external validation was assessed based on both discrimination and calibration.

Approval

The studies were approved by the institutional review boards (ethics committee) of KPNC (the University of Chicago), and GH (University of Washington). Informed consent was waived for this study since it involves secondary data analyses. The original parent studies (Diabetes & Aging, and Pathways) both obtained informed consent when the participants answered the survey.

Role of the Funding Source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report or the decision to submit the article for publication.

The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

The mean age of the development cohort was 70·6 (SD 6·8) years at baseline, 46% were female. The modal education level was trade/business school. The population was ethnically diverse, with 37% non-Caucasian. Mean diabetes duration at baseline was 11·6 (SD 9·5) years. A total of 5,173 patients (17·3%) received a dementia diagnosis during on average 6·6

years follow-up (Table 5). During follow-up, 14,366 (48%) patients died, 3,465 (24%) of whom had received a dementia diagnosis before death.

Among the 45 candidate predictors 18 met both the prevalence and the incidence rate Table 1 selection criteria. Candidate predictors not meeting the prevalence criteria, but with a markedly increased incidence rate, were merged into a single predictor (e.g. severe hypoglycemic and severe hyperglycemic events merged into acute metabolic events) and were eligible for the second selection step. The selected candidate predictors were all significantly associated with dementia in Cox proportional hazards models adjusted for age, education, race, and gender (Table 3).

The model containing age, education, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, and depression most strongly predicted ten year dementia risk. The β coefficients, the Hazard Ratios and the 95% confidence intervals of the final model are shown in table 4. The c-statistic of the final model was 0·736. The Hosmer-Lemeshow chi square showed a good calibration of 15·1 (p=0·06) . Age was used as the standardizing reference for assigning points for the risk score, with the β coefficient of five years of age (i.e. 0·57) equalling two points. The points for all predictors are relative to this. Substituting the β coefficients by points only slightly decreased the c-statistic to 0·733.

The risk of dementia is reported per sum score (Table 6). Sum scores above 11 (i.e., 12-19) were relatively rare. Consequently, risk estimates were less stable for these highest scores. Therefore, scores 12 and above were collapsed into one category for the Kaplan Meier estimated dementia risk and Cox proportional hazards model. There was a 15-fold difference in dementia risk between the lowest sum score −1 (associated Kaplan Meier estimate 5%) and the highest sum score ≥12 (associated Kaplan Meier estimate 73%). A Cox proportional hazards model (Table 6) showed that compared to those in the lowest sum score , those in the highest sum score were 37 times more likely to be diagnosed with dementia in the subsequent ten years (Hazards Ratio=37·1, 95% confidence Intervals 28·6, 48·0). The increase in dementia risk was linear as the scores increased (Table 6). Table 6 also shows that the higher the sum scores the shorter the mean time to dementia incidence. The summary of the diabetes specific dementia risk score (DSDRS) is shown in Figure 2.

Since the risk of dementia differs markedly according to age, we also analysed the observed dementia risk stratified into 5-year age brackets. Figure 3 shows the differences in observed dementia risk within age categories based on the presence of additional risk factors (expressed as higher sum score), indicating robust performance of the risk score within each of the 5-year age strata, even for the older groups.

In the external validation cohort 328 (13·6%) members received a diagnosis of dementia during an average follow-up of 6·7 years, at an average age of 78·8 at follow-up (SD 7·2) years (Table 7). Compared to the development cohort, the subjects were older, more often had a college or higher degree, a diabetic foot or microvascular disease, but less frequently had acute metabolic events, cardiovascular disease or cerebrovascular disease (Table 8). Gender distribution and the frequency of depression were comparable between the two

cohorts. In the validation cohort the risk score had a c-statistic of 0·744. The Hosmer-Lemeshow chi square shows a calibration of 6·8 with a p-value of 0·56, indicating no difference between the observed and predicted dementia risk. The risk of dementia is reported per sum score (Table 9). In the validation cohort there was a 19-fold difference in dementia risk between the lowest sum score −1 (associated Kaplan Meier estimate 3%) and the highest sum score ≥12 (associated Kaplan Meier estimate 57%).

Discussion

The diabetes specific dementia risk score (DSDRS) presented in this paper predicts an individual's absolute risk of developing dementia within the subsequent decade based on diabetes-related comorbidities and complications, age, and education. The predictive accuracy of the DSDRS in the development and validation cohort was comparable. The DSDRS stratifies individuals into 14 categories from −1 to ≥12, showing a 15-fold difference in dementia risk between the lowest and the highest sum score and performs well in all age categories (Figure 4).

The DSDRS is a practical tool. All included predictors are easy to assess and readily available in a primary care setting. More importantly, no additional labour-intensive or expensive tests, such as cognitive testing or brain imaging, are required. Some of the predictors included in the final model are end-organ complications. This is likely reflective of prolonged exposure to dysglycemia and cardiovascular risk factors and susceptibility to the adverse effects of these factors. In contrast, HbA1c and diabetes duration were not included in the final model, as their predictive value was lower than that of the end-organ complications. The identification of new predictors particular to the diabetic condition (such as cardiovascular disease and diabetic foot) in this study (see research in context panel), emphasizes the importance of creating a risk score specifically for patients with T2DM

A major strength of this study is the large diverse cohort of diabetic patients with ten years of follow-up, and detailed data on comorbid conditions, including complications of T2DM. The opportunity to conduct an external validation in another well-defined large T2DM cohort in a different geographical location corroborates the findings. The differences in distribution of the predictors in the development and validation cohort (Table 8), did not influence the predictive accuracy of the DSDRS in the validation cohort, emphasizing that the DSDRS is robust and not based on overfitting the development cohort data. Nevertheless, the underlying population structure of our two cohorts could also have impacted results. Our development and validation cohorts are based on patients with equal access to medical care, reducing the bias of medical care access, however the results may not be reflective of populations that are uninsured, or to countries with more limited health care resources. There are several limitations to our study. One weakness is the use of medical record diagnoses for dementia and other comorbidities. However, our algorithm for dementia was previously shown to have a sensitivity of 77% and specificity of 95% compared to a consensus diagnosis of dementia; based on a neuropsychiatric battery, physical examination, structured interview with informants, and review of medical records.[15] Although the list of 45 candidate predictors is extensive, there may be other predictors that could further improve the predictability of the model such as dementia-

associated biomarkers (e.g. APOE genotype, MRI abnormalities) or cognitive tests. Future studies could incorporate a step-wise model, where patients are first selected on readily available predictors contained in the DSDRS after which additional labour intensive tests are performed.

In contrast to diagnostic models, prognostic models are –by definition- created to predict future risk. Because of their stochastic nature, the estimated probabilities are of primary interest. Both discrimination and calibration are essential components of model evaluation[27]. Apart from accuracy, the practical value of a prediction model depends on other items, such as the potentials for extrapolation, relevance of the outcome, and usability [28]. The DSDRS has a slightly higher predictive ability in the validation cohort, which might be explained by the relatively smaller sample size of that cohort.[29] The discriminative ability of the DSDRS (c-statistic 0·733-0·744) is higher or equal to that of other commonly used risk scores that rely on similar, readily available clinical predictors, such as the CHADS2 (0·70[7]) or Framingham cardiovascular risk score (0·68[6]). Calibration data on these latter scores have not been reported. There are also some published risk scores for dementia (see research in context panel), but these were created with different approaches, aims, and target populations – i.e. not specifically addressing diabetes - than the present study. One study predicted late life dementia risk using sociodemographic and cardiovascular risk factors in midlife[11], with a discriminative ability equivalent to the DSDRS. However, the long interval between the risk assessment and the outcome makes the applicability of this midlife score in directing preventive treatment quite different to the DSDRS. Compared to three other previously published late-life dementia risk scores (c-statistic 0·82[8] 0·84 [9] 0·79[10]; calibration not reported), the DSDRS has a slightly lower discrimination. Nevertheless, by comparison, the performance of the DSDRS is robust considering the simplicity of its predictors (the other scores included cognitive testing[9], biomarkers[8,10], or brain imaging[8]), and the longer prediction period of the DSDRS. Most importantly, the DSDRS is the *only* risk score specifically targeting older people with T2DM, a population particularly vulnerable to dementia.

Early detection of diabetic patients at increased risk of dementia may help to develop and target preventive treatment. Currently, one in ten to fifteen cases of dementia is attributable to diabetes, making it an obvious target for dementia prevention.[30] Recently, the first large trial that specifically targeted cognition in older people with T2DM, the ACCORD-MIND[31], showed that intensive glucose lowering treatment over 40 months in people older than 55 years with T2DM, did not benefit cognitive performance. It has been suggested that the relatively young age of the sample (average 62 years), the limited decline in cognitive performance during follow-up, and short treatment duration could possibly explain the lack of treatment effect.[30] This example highlights the importance of the *timing* of intervention and the need for selection of high risk patients, suggesting a promising role for future application of the DSDRS.

Unfortunately there is an epidemic of both diabetes and dementia, and the linkage between these two conditions portends a possible public health crisis. The present findings demonstrate that in two large populations of patients with T2DM a combination of diabetes-associated complications, education, and age is highly predictive of the likelihood of

dementia within the next decade. The DSDR could be instrumental in selection of high risk patients for early intervention studies as well as numerous applications of personalized medicine. The DSDR can guide clinician's decisions regarding increased clinical attention, cognitive screening and the potential for dangerous diabetes treatment-associated side effects associated with cognitive impairment, such as hypoglycemia.

Acknowledgements

Funding: The United States National Institute of Health (R01 DK081796, RAW, EH, AJK; P30 DK092949 EH; P30 DK092924 AJK), Kaiser Permanente Community Benefits (RAW, JRM). High potential grant from Utrecht University, VIDI grant 91711384 from ZonMw, The Netherlands Organisation for Health Research and Development (GJB LGE). LGE is also supported by a Fulbright fellowship.

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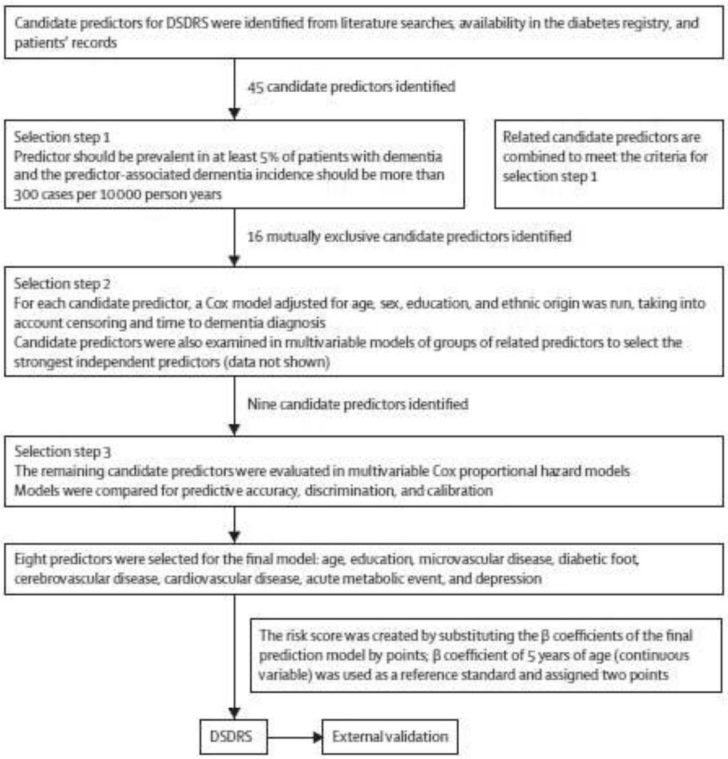

Figure 1.
Flow-chart of the analytic steps of creating the DSDRS.

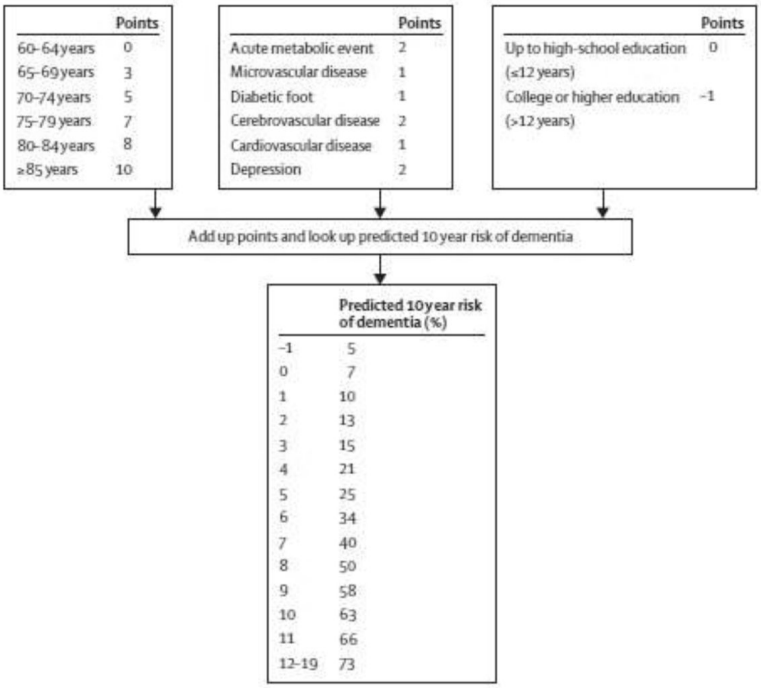

Figure 2.

Summary of the diabetes-specific dementia risk score According to the figure, a 71-year-old man with a university degree and a medical history of diabetes type 2, diabetic retinopathy, and myocardial infarction would have a diabetes-specific dementia risk score of 6 points and therefore a 34% risk of dementia in the next 10 years; an 86-year-old woman with a high-school education and type 2 diabetes and depression would have a risk score of 11 points and a 66% risk of dementia in the next 10 years; and a 61-year-old man who did not complete high school, and had type 2 diabetes, diabetic foot, several hospital admissions for severe hypoglycaemic events, a stroke, and depression would have a risk score of seven points and a 40% risk of dementia in the next 10 years.

	ALL		AGE											
			60-64		65-69		70-74		75-79		80-84		>85	
Percentiles	DSDRS points	DR %	DSDRS points	DR %	DSDRS points	DR %	DSDRS points	DR %	DSDRS points	DR %	DSDRS points	DR %	DSDRS points	DR %
P90	9	58%	2	12%	5	25%	8	44%	10	58%	11	63%	12	76%
P75	7	40%	1	10%	4	21%	6	32%	9	56%	10	68%	12	76%
Median	4	21%	0	7%	3	14%	5	25%	7	41%	8	62%	10	66%
P25	2	13%	-1	5%	2	13%	5	25%	7	41%	8	62%	10	66%
P10	0	7%	-1	5%	2	13%	4	21%	6	37%	7	47%	10	66%
Mean (±SD)	4·5(±3·3)		0·3(±1·4)		3·5(±1·5)		5·6(±1·5)		7·7(±1·5)		8·8(±1·4)		10·6(±1·1)	

Figure 3. Observed dementia risk (DR) per sum score (SS) stratified by age groups

Mean points (±SD). Pnumber represents percentiles, P90 is 90th percentile.

Shown is the distribution based on the number of subjects with a certain amount of points. The associated dementia risk (DR) based on Kaplan-Meier estimates per sum score of the diabetes specific dementia risk score (DSDRS) is reported.

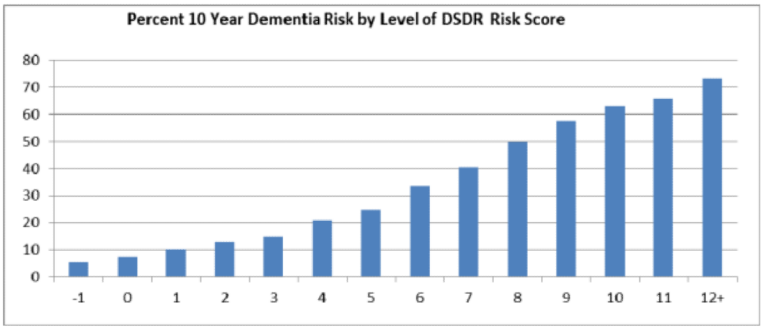

Figure 4.
Ten year dementia risk by levels of DSDR categories in the development cohort

Table 1

Prevalence and incidence rate of the 45 candidate predictors in step one of the selection process

Variable		Prevalence in dementia cases	Incidence rate per 10.000 Person Years
Age (years)	< 65	465 (9%)	82·9
	65-69	983 (19%)	169·5
	70-74	1345 (26%)	294·1
	75-79	1351 (26%)	508·1
	80-84	763 (15%)	815·9
	85-89	223 (4%)	1001·1
	≥90	43 (<1%)	1152·6
Gender	Men	2566 (50%)	244·4
Ethnicity	White	3342 (65%)	277·9
	African Am.	670 (13%)	287·3
	Hispanic	508 (10%)	213·7
	Asian	441 (9%)	184·3
	Native. Am	131 (3%)	315·3
	Other	18 (<1%)	186·2
Education	<9 y	556 (12%)	356·6
	9-11 y	627 (13%)	305·9
	High school	482 (31%)	271·1
	Some college	1145 (24%)	232·9
	College grad	392 (8%)	212·0
	Grad school	534 (11%)	222·2
Time since T2DM diagnosis	≤5 y	1110 (22%)	213·5
	5-10 y	1645 (32%)	250·1
	> 10 y	2332 (46%)	298·7
Age at T2DM diagnosis	<50	580 (11%)	226·0
	50-59	1161 (23%)	162·7
	60-69	2302 (45%)	266·4
	≥70	1044 (21%)	571·8
Severe hyperglycaemic event		28 (<1%)	662·1
Severe hypoglycaemia event		230 (4%)	516·6
DM treatment	No medication	939 (18%)	242·5
	Insulin only	1082 (21%)	299·1
	Oral only	2847 (55%)	255·2
	Insulin & oral	305 (6%)	256·1
Diet		3240 (63%)	256·2
Physical exercise		2591 (50%)	237·6
HbA1c (glycosylated hemoglobin) (%)	<5	54 (0.2%)	361·6

Variable		Prevalence in dementia cases	Incidence rate per 10.000 Person Years
	5-10	23135 (88%)	258·4
	10-12	2239 (9%)	247·8
	>12	988 (4%)	237·9
BMI (kg/m^2)	<18.5	39 (1%)	425·1
	18.5-24.99	1239 (27%)	327·8
	25-29.99	1949 (42%)	261·4
	>30	1385 (30%)	209·4
Smoking	Current	305 (7%)	218·6
	Former	2066 (44%)	253·7
	Never	2354 (50%)	270·1
Alcohol	Current	1994 (44%)	221·5
	Former	1404 (31%)	289·0
	Never	1178 (26%)	295·2
Hospitalization ≥1		1418 (27%)	380·3
Number of medications	≥4	3332 (64%)	294·4
Anti-hypertensives		3624 (70%)	276·1
Anti-lipemics		923 (18%)	270·6
Antiepileptic agents		132 (3%)	223·6
Neuroleptics		64 (1%)	557·2
Benzodiazepine		419 (8%)	402·0
Antiarrhythmics		101 (2%)	370·4
Digoxin		577 (11%)	437·9
Antidepressive agents past 2 years		1280 (25%)	362·7
Depression diagnosis		619 (12%)	431·1
Diabetic retinopathy		166 (3%)	320·7
Diabetic macular edema		295 (6%)	365·1
End stage renal disease		36 (<1%)	600·6
Dialysis		35 (<1%)	613·2
Kidney transplantations		6 (<1%)	347·0
Coronary artery bypass grafting		112 (2%)	265·3
Congestive heart failure		635 (12%)	419·6
Stroke/TIA		531 (10%)	537·7
Percutaneous transluminal coronary angioplasty		300 (6%)	248·8
Myocardial infarction		733 (14%)	325·9
Carotid endarterectomy		108 (2%)	414·9
Peripheral endarterectomy		17 (<1%)	415·1
Precerebral artery disease		168 (3%)	448·4
Peripheral vascular disease		372 (7%)	467·6

Variable		Prevalence in dementia cases	Incidence rate per 10.000 Person Years
Hypertension diagnosis		3128 (61%)	274·9
Hyperlipidaemia diagnosis		954 (18%)	216·8
Head trauma		7 (<1%)	601·0
Lower extremity amputation		105 (2%)	455·7
Gangrene or lower limb ulcer		245 (5%)	457·8
Merged predictors [#]			
Diabetic foot[b]		251 (5%)	454·0
Acute metabolic event [c]		250 (5%)	535·0
Depression [c]		1422(28%)	367·6
Microvascular disease[c]		412 (8%)	338·6
Cardiovascular disease[b]		1386 (27%)	352·2
Cerebrovascular disease[b]		534 (10%) 5	38·0

[#]Definitions merged predictors:
Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation;
Acute metabolic events = severe hyper- and/or hypoglycemic events;
Microvascular disease = diabetic retinal disease and/or end-stage-renal disease (including dialysis and kidney transplantation);
Cardiovascular disease = peripheral arterial disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure;
Cerebrovascular disease = stroke/transient ischemic attack, precerebral arterial disease, and/or carotid endarterectomy.

[b]based on medical history 1979-1997 (b) or 1996-1997 (c).

[c]based on medical history 1979-1997 (b) or 1996-1997 (c).

Table 2

Diagnostic Codes for several comorbidities.

Category	Specific disease or treatment	ICD-9 CM Codes	CPT-codes	Medication use
Diabetic foot	Gangrene or lower limb ulcer that required hospitalization	785.4, 440.23, 440.24, 250.7, 0.40.0, 892.1, 707.1		
	Lower extremity amputation	84.10-84.17	27598-27882, 27884, 27886, 27888-28800, 28805, 28820, 28825, 28810, 27290, 27295;	
Acute metabolic event	Hyperglycemia severe enough to be hospitalized	250.1,250.2, 249.2		
	Hypoglycemia severe enough to be hospitalized	251.0-2		
Depression		296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 309.28, 311.x		Amitriptyline, Bupropion, Desipramine. Doxepin, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Protriptyline, Sertraline, Tranylcypromine, Trazodone, Trimipramine, Venlafaxine
Microvascular disease	Diabetic retinal disease	250.5, 362.02250.5, 362.53, 362.83	67228 67208 67210	
	End-stage renal disease	ascertained by matching with the US Renal Data System registry		
Cardiovascular Events	Peripheral arterial disease	440.x (without 440.23 440.24), 441.x , 442.0, 442.3, 443.81 (if underlying disease is DM), 443.9		
	Myocardial infarction	410, 412, 401		
	Coronary artery bypass graft	36.01; 36.02; 36.05	92982, 92984, 93570	
	Percutaneous transluminal coronary angioplasty	6.10; 36.11; 36.12; 36.13; 36.14, 36.15; 36.16; 36.19	33510-33516	
	Congestive hear failure	401.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13,		

Category	Specific disease or treatment	ICD-9 CM Codes	CPT-codes	Medication use
		404.93, 428.0, 428.1, 428.9, 4251		
Cerebrovascular disease	Cerebrovascular attacks	431, 433, 434, 436, 442.81, 442.82, 433.x		
	Precerebral arterial disease	442.81, 442.82, 433.x		
	Carotid endarterectomy	38.11, 38.12	35301, 35390, 35501, 35506, 35507, 35508, 35509	
Hypertension		401-405		
Hyperlipidemia		272		
Head trauma		3102, 3109, 3509, 7390, 8030, 8500-8502, 8505, 8509, 8522, 8540, 9519, 9529, 7722, 80300, 80350, 80390, 85011, 85012, 85180, 85201, 85220, 85240, 85241, 85300, 85400, 85401, 85409, 85410, 95901, 43889, 854, 430		

All covariates were defined between 1996-1998, except for cardiovascular disease, cerebrovascular disease and diagnoses of head trauma they were collected between January 1, 1979 – December 31, 1997.

Table 3

Incidence rate of dementia and adjusted hazard ratio of the candidate predictors selected after step 1.x

	Incidence rate of dementia			Adjusted hazard ratio		
	No. of Dementia cases	**Total Person Years**	**Incidence Rate per 10.000 Person Years (95%CI)**	**HR**	**95%CI**	**β**
Sociodemographic				Base model		
Age, y				1·12*	1·12 - 1·13	0·11
60-64	465	56092	82·90 (75·36 - 90·43)			
65-69	983	57993	169·50 (158·91 - 180·10)			
70-74	1345	45736	294·08 (278·36 - 309·79)			
75-79	1351	26590	508·07 (480·98 - 535·17)			
80-84	763	9352	815·85 (757·96 - 873·74)			
85-90	223	2227	1001·12 (869·72 - 1132·51)			
>90	43	373	1152·63 (808·11 - 1497·15)			
Male	2566	105012	244·35 (234·90 - 253·81)	0·97*	0·91 - 1·02	−0·03
Female	2607	93352	279·26 (268·54 - 289·98)			
Race/ethnicity (n= 29665)						
White	3342	120279	277·85 (268·43 - 287·27)	ref		
African American	670	23321	287·29 (265·54 - 309·05)	1·22*	1·12 - 1·33	0·20
Hispanic	508	23770	213·71 (195·12 - 232·29)	0·94	0·85 - 1·05	−0·06
Asian	441	23930	184·28 (167·08 - 201·48)	0·82*	0·73 - 0·91	−0·20
Native American	131	4154	315·29 (261·30 - 369·29)	1·29*	1·07 - 1·54	0·25
Other	18	966	186·20 (100·18 - 272·23)	0·89*	0·54 - 1·45	−0·12
Education (n= 27516)						
<9 y	556	15590	356·63 (326·99 - 386·28)	Ref		
9-11y	627	20498	305·88 (281·93 - 329·82)	0.87	0.77 - 0.98	−0.14
High school	1482	54660	271·13 (257·32 - 284·93)	0.75	0.68 - 0.83	−0.28
Some college	1145	49157	232·93 (219·43 - 246·42)	0.65	0.59 - 0.72	−0.43
College grad	392	18491	211·99 (191·01 - 232·98)	0.59	0.52 - 0.67	−0.53
Grad school	534	24032	222·20 (203·35 - 241·04)	0.61	0.54 - 0.69	−0.50
Separate models						

	Incidence rate of dementia			Adjusted hazard ratio		
	No. of Dementia cases	**Total Person Years**	**Incidence Rate per 10.000 Person Years (95%CI)**	**HR**	**95%CI**	**β**
per candidate predictor ^						
BMI (kg/m^2)						
<18.5	39	917	425.14 (291.71 - 558.58)	1.40	1.02 - 1.93	0.34
18.5-24.99	1239	37801	327.76 (309.51 - 346.01)	Ref		
25-29.99	1949	74547	261.45 (249.84 - 273.05)	0.86	0.80 - 0.92	−0.16
>30	1385	66131	209.43 (198.4 - 220.46)	0.81	0.75 - 0.88	−0.21
Hospitalization in 1996-1997	1418	37287	380.29 (360·49 - 400·08)	1·76*	1·60 1·94	0·40
Diabetes specific						
T2DM duration						
≤5 years	1110	51991	213·50 (200·94 - 226·06)	ref		
5-10 years	1645	65773	250·10 (238·01 - 262·19)	1·17*	1·08 - 1·27	0·16
> 10 years	2332	78062	298·74 (286·61 - 310·86)	1·30*	1·20 - 1·40	0·26
T2DM age at diagnosis						
<50 years	580	25662	226.01 (207.62 - 244.41)	1.36	1.21 1.53	0.31
50-59 years	1161	71365	162.68 (153.33 - 172.04)	1.15	1.03 - 1.27	0.14
60-69 years	2009	75418	266.38 (254.73 - 278.03)	1.05	0.96 - 1.15	0.05
≥ 70 years	1337	23381	571.83 (541.18,602.48)	Ref		
HbA1c (%)						
<5	12	331	361·61 (157·01 - 566·21)	1·43	0·81 - 2·53	0·36
5-10	3999	154756	258·41 (250·40 - 266·42)	ref		
10-12	372	15013	247·78 (222·60 - 272·96)	1·20*	1·07 - 1·35	0·18
>12	154	6472	237·92 (200·34 - 275·50)	1·32*	1·11 - 1·57	0·28
Diabetes treatment type						
Insulin only	939	38730	242·45 (226·94 - 257·95)	1·43*	1·30 - 1·56	0·36
Oral only	1082	36177	299·08 (281·26 - 316·90)	1·15*	1·06 - 1·24	0·14
Insulin and oral agents	2847	111547	255·23 (245·85 - 264·60)	1·38*	1·20 - 1·58	0·32
No pharmacological controlled	305	11910	256·08 (227·34 - 284·81)	ref		

	Incidence rate of dementia			Adjusted hazard ratio		
	No. of Dementia cases	**Total Person Years**	**Incidence Rate per 10.000 Person Years (95%CI)**	**HR**	**95%CI**	**β**
Diabetic foot [a]	251	5529	453·95 (397·79 - 510·11)	1·99*	1·75 - 2·28	0·69
Acute metabolic event[b]	250	4673	534·98 (468·66 - 601·30)	1·88*	1·65 - 2·16	0·63
Comorbid diseases						
Depression[b]	1422	38684	367·59 (348·49 - 386·70)	1·65*	1·55 - 1·77	0·50
Microvascular disease[b]	412	12166	338·64 (305·94 - 371·34)	1·48*	1·33 - 1·64	0·39
Cardiovascular disease[a]	1386	39349	352·23 (333·69 - 370·77)	1·42*	1·33 - 1·51	0·35
Cerebrovascular disease[a]	534	9925	537·99 (492·36 - 583·62)	1·91*	1·73 - 2·10	0·64
Benzodiazepam use	419	10423	401.99 (363.50 – 440.49)	1.44	1.30 - 1.60	0.37
Digoxin use	577	13178	437.85 (402.12 – 473.58)	1.42	1.30 - 1.56	0.35

This tables shows the 16 mutually exclusive candidate predictors that are selected after step 1, in addition it shows gender and race because the Cox proportional hazard models were all adjusted for age, gender, ethnicity and education. 2,628 subjects form the total cohort of 29,961 were not included in the Cox proportional hazard models because of missing values on education or race.

HR = Hazard Ratio; CI = Confidence Interval; β= beta-coefficient.

*p values < 0·05

^The models were adjusted for age, gender, race and education.

[a]based on medical history 1979-1997 (a) or 1996-1997 (b)

[b]based on medical history 1979-1997 (a) or 1996-1997 (b)

Definitions: Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation;
Acute metabolic events = severe hyper- and/or hypoglycemic events;
Microvascular disease = diabetic retinal disease and/or endstage-renal disease;
Cardiovascular disease = peripheral arterial disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure;
Cerebrovascular disease = cerebrovascular attacks, precerebral arterial disease, and/or carotid endarterectomy.

Table 4

Final multivariable model of the diabetes specific dementia risk score.

n = 27512[#]		β	HR (95%CI)	Risk score
Age	60-64	0	1	0
	65-69	0·73*	2·08 (1·85 2·33)	3
	70-74	1·28*	3·61 (3·23 4·03)	5
	75-79	1·87*	6·51 (5·82 7·27)	7
	80-84	2·39*	10·94 (9·68 12·36)	8
	>85	2·73*	15·41 (13·12 18·09)	10
Education	High school or less	0	1	0
	College or more	−0·14*	0·87 (0·82 0·92)	−1
Microvascular disease [a]	Yes	0·28*	1·33 (1·19 1·48)	1
	No	0	1	0
Diabetic foot [a]	Yes	0·40*	1·50 (1·30 1·72)	1
	No	0	1	0
Cerebrovascular disease [a]	Yes	0·50*	1·65 (1·50 1·82)	2
	No	0	1	0
Cardiovascular disease [a]	Yes	0·19*	1·21 (1·13 1·29)	1
	No	0	1	0
Acute metabolic event [b]	Yes	0·45*	1·58 (1·37 1·81)	2
	No	0	1	0
Depression [b]	Yes	0·46*	1·58 (1·48 1·69)	2
	No	0	1	0

β = beta coefficient from Cox proportional hazards model; HR = Hazard Ratio; CI = confidence interval Definitions: Microvascular disease = diabetic retinal disease and/or end-stage-renal disease; Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation; Cerebrovascular disease = cerebrovascular attacks, precerebral arterial disease, and/or carotid endarterectomy; Cardiovascular disease = peripheral arterial disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure; Acute metabolic events = severe hyper- and/or hypoglycemic events.

[#] 2,449 subjects form the total cohort of 29,661 were not included in the models because of missing values on education or race.

* p value <·0001

[a] based on medical history 1979-1997 (a) or 1996-1997 (b).

[b] based on medical history 1979-1997 (a) or 1996-1997 (b).

Table 5

Baseline population characteristics of the development cohort by incident dementia status.

	No dementia N=24788	Dementia N=5173	p value
Sociodemographic			
Age, y	69·7 (±6·5)	74·2 ± (6·6)	<0·0001
Male	13611 (55%)	2566 (50%)	<0·0001
Race/ethnicity (n= 29665)			<0·0001
White	15562 (63%)	3342 (65%)	
African American	2730 (11%)	670(13%)	
Hispanic	2785 (11%)	508 (10%)	
Asian	2807 (11%)	441 (9%)	
Native American	550 (2%)	131 (3%)	
Other	121 (0·5%)	18 (0·4%)	
Education (n= 27516)			<0·0001
High school or less	11417 (50%)	2665 (56%)	
College or more	11363 (50%)	2071 (44%)	
Hospitalization in 1996-1997	5644 (23%)	1418 (27%)	<0·0001
KPNC membership duration, y	14·2 (±5)	15·0 ± (4·7)	<0·0001
Diabetes specific			
T2DM duration, y	8·0 (IQR 9·8)	8·9 (IQR 11·3)	<0·0001
HbA1c, in %	7·8 (±1·8)	7·7 (±1·8)	0·004
Diabetes treatment type			0·002
Nonpharmacological-controlled	4995 (20%)	939 (18%)	
Insulin only	4823 (19%)	1082 (21%)	
Oral only	13400 (54%)	2847 (55%)	
Insulin and oral agents	1570 (6%)	305 (6%)	
Diabetic foot [a]	1061 (4%)	251 (5%)	0·07
Acute metabolic event [b]	783 (3%)	250 (5%)	<0·0001
Comorbid diseases			
Depression [b]	5139 (21%)	1422 (27%)	<0·0001
Microvascular disease [b]	1749 (7%)	412 (8%)	0·02
Cardiovascular disease [a]	6178 (25%)	1386 (27%)	0·005
Cerebrovascular disease [a]	1615 (7%)	534 (10%)	<0·0001
Head trauma [a]	89 (0·4%)	37 (0·7%)	0·003

Presented are demographics, key diabetes relates variables and all predictors included in the final model, the other variables are included in Table 1.

Data are presented as number (%) or mean (±SD).

p values were calculated using chi-square or student t-test.

Definitions: Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation; Acute metabolic events = severe hyper- and/or hypoglycemic events; Microvascular disease = diabetic retinal disease and/or end-stage-renal disease; Cardiovascular disease = peripheral arterial

disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure; Cerebrovascular disease = cerebrovascular attacks, precerebral arterial disease, and/or carotid endarterectomy.

[a] based on medical history 1979-1997 (a) or 1996-1997 (b).

[b] based on medical history 1979-1997 (a) or 1996-1997 (b).

Table 6

Dementia risk by each level of the risk score.

Sum score	Number at risk[a]	Dementia cases[b]	Hazard ratio[c]	Mean time to incident dementia	Observed ten year dementia risk[d]
	N (%)	N (%)	HR (95%CI)	Mean in y (±SD)	% (95% CI)
−1	2234 (8·1%)	92 (4·1%)	Ref	9·8 (±0·1)	5·3 % (4·2 6·3)
0	2128 (7·7%)	118 (5·5%)	1·4 (1·1 1·8)	9·7 (±0·1)	7·4 % (6·1 8·6)
1	1030 (3·7%)	72 (7·0%)	2·0 (1·5 2·7)	9·5 (±0·1)	9·9% (7·7 12·1)
2	2798 (10·2%)	273 (9·8%)	2·5 (2·0 3·2)	9·5 (±0·1)	12·9% (11·4 14·3)
3	2810 (10·2%)	305 (10·9%)	2·9 (2·3 3·7)	9·4 (±0·1)	14·8% (13·2 16·3)
4	2860 (10·4%)	434 (15·2%)	4·5 (3·6 5·6)	9·1 (±0·1)	21·0% (19·2 22·8)
5	3218 (11·7%)	550 (17·1%)	5·2 (4·2 6·5)	9·0 (±0·1)	24·5% (22·7 26·3)
6	2416 (8·8%)	550 (22·8%)	8·0 (6·4 10·0)	8·5 (±0·1)	33·5% (31·1 35·9)
7	2907 (10·6%)	751 (25·8%)	9·7 (7·8 12·0)	8·3 (±0·1)	40·3% (37·9 42·7)
8	1930 (7·0%)	555 (28·8%)	13·6 (10·9 17·0)	7·7 (±0·2)	49·9% (46·6 53·2)
9	1287 (4·7%)	422 (32·8%)	18·0 (14·3 22·5)	7·0 (±0·2)	57·5% (53·3 61·7)
10	979 (3·6%)	320 (32·7%)	21·2 (16·8 26·7)	6·6 (±0·2)	63·1% (58·0 68·2)
11	466 (1·7%)	135 (29·0%)	24·0 (18·4 31·3)	6·4 (±0·4)	65·8% (56·0 75·6)
12-19	449 (1·6%)	159 (34·7%)	37·1 (28·6 48·0)	5·2 (±0·4)	73·3% (64·8 81·8)

[a] Number at risk: number of subjects within each sum score group, with percentage of the total cohort in brackets.

[b] Number of dementia cases in this sum score group: the percentage is the proportion of persons with incident dementia in that particular sum score group.

[c] from Cox proportional hazards model.

[d] based on Kaplan Meier estimates.

Table 7

External validation cohort: population characteristics by incident dementia status.

	No dementia N=2085	Dementia N=328	p value
Sociodemographic			
Age, y	71·3 (±7·3)	77·0 (±6·5)	<0·0001
Male	1135 (54%)	161 (49%)	0·07
Education			
High school or less	613 (30%)	119 (37%)	
College or more	1445 (70%)	204 (63%)	0·01
Diabetes specific			
Diabetes treatment type			0·74
Nonpharmacological-controlled	594 (28%)	95 (29%)	
Oral only	915 (44%)	137 (42%)	
Insulin (incl. combination with oral agents)	576 (28%)	96 (29%)	
Diabetic foot[a]	121 (6%)	20 (6%)	0·83
Acute metabolic event[a]	0	0	
Comorbid diseases			
Depression[a]	402 (20%)	97 (30%)	<0·0001
Microvascular disease[a]	196 (9%)	41 (13%)	0·07
Cardiovascular disease[a]	244 (12%)	56 (17%)	0·006
Cerebrovascular disease[a]	45 (2%)	12 (4%)	0·09

Data are presented as number (%) or mean (±SD).

p values were calculated using chi-square or student t-test.

Definitions: Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation; Acute metabolic events = severe hyper- and/or hypoglycemic events; Microvascular disease = diabetic retinal disease and/or end-stage-renal disease; Cardiovascular disease = peripheral arterial disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure; Cerebrovascular disease = cerebrovascular attacks, precerebral arterial disease, and/or carotid endarterectomy.

[a]based on medical history or identification 6 months prior to baseline 01/03/2001 and 01/09/2002

Table 8

Comparison of the DSDRS predictors in the development and validation cohort.

	Development cohort N= 29961	**Validation cohort N=2413**	**p value**
Sociodemographic			
Age, y	70·6 ±6·8	72·1 ±7·1	<0·0001
Male	16177 (54%)	1296 (54%)	0·80
Education			
High school or less	14082 (51%)	732 (31%)	<0·0001
College or more	13434 (49%)	1649 (69%)	<0·0001
Diabetes specific			
Diabetic foot	1312 (4%) c	141 (6%) b	0·001
Acute metabolic event	1033 (3%) *a*	0*b*	<0·0001
Comorbid diseases			
Depression	6561 (22%) *a*	499 (21%) *b*	0·17
Microvascular disease	2161(7%) *a*	237 (10%) *b*	<0·0001
Cardiovascular disease	7564 (25%) *c*	300 (12%) *b*	<0·0001
Cerebrovascular disease	2149(7%) *c*	57 (2%) *b*	<0·0001

Data are presented as number (%) or mean (±SD).

p values were calculated using chi-square or student t-test.

Definitions:
Diabetic foot = gangrene, lower limb ulcer, and/or lower extremity amputation;
Acute metabolic events = severe hyper- and/or hypoglycemic events;
Microvascular disease = diabetic retinal disease and/or endstage-renal disease;
Cardiovascular disease = peripheral arterial disease, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or congestive heart failure;
Cerebrovascular disease = cerebrovascular attacks, precerebral arterial disease, and/or carotid endarterectomy.

a based on medical history 1979-1997

b based on medical history or identification 6 months prior to baseline 01/03/2001 and 01/09/2002

c based on medical history 1996-1997 .

Table 9

Dementia risk by each level of the risk score in the validation cohort.

Sum score	Number at risk[a]	Dementia cases[b]	Mean time to incident dementia	Observed ten year dementia risk[c]
	N (%)	N (%)	Mean in y ±SD	(95% CI)
−1	230(9·5%)	4 (1·7%)	9·5 ±0·0	3% (1 -7)
0	85 (3·5%)	4 (4.7%)	7·4 ±0·1	7% (3 -18)
1	90 (3·7%)	3 (3·3%)	7·2 ±0·1	4% (1-12)
2	268 (11·1%)	8 (3·0%)	9·4 ±0·1	4% (2-8)
3	125 (5·2%)	9 (7.2%)	7·8 ±0·1	9% (5-16)
4	294 (12·2%)	25 (8.5%)	9·1 ±0·1	11% (8-16)
5	215 (8·9%)	28 (13.0%)	8·8 ±0·1	17% (12-24)
6	289 (12·0%)	50 (17.3%)	8·9 ±0·2	26% (20-33)
7	317 (13·1%)	53 (16.7%)	8·7 ±0·2	22% (17-29)
8	181 (7·5%)	42 (23.2%)	8·2 ±0·2	36% (28-46)
9	139 (5·8%)	43 (30.9%)	7·3 ±0·3	50% (29-62)
10	100 (4·1%)	34 (34.0%)	6·4 ±0·4	64% (47-82)
11	27 (1·1%)	11 (40.7%)	6·1±0·7	61% (37-86)
12-19	21 (0·69%)	9 (42·9%)	3·5 ±0·5	58% (32-86)

[a] Number at risk: number of subjects within each sum score group, with percentage of the total cohort in brackets.

[b] Number of dementia cases in this sum score group: the percentage is the proportion of persons with incident dementia in that particular sum score group.

[c] based on Kaplan-Meier estimates.