Skin autofluorescence improves the Finnish Diabetes Risk Score in the detection of diabetes in a large population based cohort – the LifeLines cohort study

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Abstract

Purpose

In type 2 diabetes mellitus, a long, clinically latent period often exists in which diabetes is not yet detected, but silent development of micro- and macrovascular complications frequently occurs. The aim of the present study was to investigate whether skin autofluorescence (SAF) would further improve the Finnish diabetes risk score (FINDRISC) in detecting undiagnosed diabetes in a large population based cohort.

Methods

Subjects included were participants of the Lifelines cohort study. SAF was assessed in an unselected subset of participants using the AGE reader. After exclusion of participants with previously diagnosed diabetes (n=1635), pregnant women (n=58), and participants using corticosteroids (n=345), 79,248 subjects were available for analysis. Diabetes was defined by fasting blood glucose ≥7.0 mmol/l, non- fasting blood glucose ≥11.1 mmol/l, or HbA1c ≥6.5%.

Results

Diabetes was detected in 1042 participants (aged 55 ± 12; 54% male). SAF improved the area under the receiver operating curve (AUROC) of the FINDRISC model from 0.802 to 0.811 ($p<0.001$). Furthermore, the addition of SAF to the FINDRISC reclassified 8 -15% of all participants into more accurate risk categories (NRI = 0.080, 95% CI 0.052 – 0.110). The proportion of participants reclassified was especially high (>30%) among the intermediate risk categories. When SAF was added to a simplified model (using age and BMI categories only), the performance of this model was similar to the full model + SAF (AUROC =0.806, $p=0.062$).

Conclusion

SAF is a non-invasive tool that may be used to further improve the FINDRISC in diabetes detection. The new model is especially useful in reclassifying participants in intermediate risk categories in which additional blood glucose testing is needed to confirm the presence of diabetes. Furthermore, a simplified model was tested that did not affect the discriminative value of the full model.

Introduction

Together with population growth and ageing, both the decrease of physical activity and the increase in obesity have led to a significant increase in the number of adults with diabetes: from 108 million in 1980 to 422 million in 2014.[1] It has been estimated that approximately 40% of people with diabetes are unaware of their disease[2] and that the mean time between diabetes development and its diagnosis is approximately 5 years. In these persons with mainly type 2 diabetes (T2DM), silent development of micro- and macrovascular complications frequently occurs which may be prevented or delayed by early screening of high risk individuals.[3]

A variety of approaches has been proposed to identify individuals with (an increased risk of) diabetes. The Finnish Diabetes Risk Score (FINDRISC) is currently the most validated and widely used.[4] It is a simple, safe, and inexpensive screening test that has been developed to predict drug-treated T2DM and to increase awareness of modifiable risk factors and the benefits of a healthy lifestyle.[5]

Skin autofluorescence (SAF) has also been proposed to be useful as a cost-effective, simple, and reproducible test for diabetes screening.[6] SAF is a clinical tool that non-invasively assesses advanced glycation endproducts (AGEs) in the skin of the forearm.[7,8] AGEs are formed by the non-enzymatic modification of proteins, lipids, or nucleic acids by reducing sugars or reactive carbonyl compounds.[9,10] Accumulation of AGEs occurs during general ageing in healthy individuals, but at an advanced rate in subjects with impaired renal function or diabetes, as a result of oxidative and glycaemic stress.[11–13] Besides the increasing evidence from clinical studies that AGEs and SAF serve as potential biomarkers for diabetic complications,[11,14] SAF has been shown to be comparable or superior to HbA1c and fasting plasma glucose in the detection of diabetes in intermediate risk groups.[15,16] However, it was pointed out that the predictive value of SAF in lower risk groups was still needed.

The aim of the present study was to establish the combined performance of the FINDRISC and SAF in detecting undiagnosed diabetes. Furthermore, it was investigated whether a simplified model could be found that would have a similar performance as the full model. Finally, this study focused on the identification of optimal cut-off values of the FINDRISC (+ SAF) for the general Dutch population.

Methods

Study population

Subjects included in this study were participants from the Lifelines Cohort Study,[17] a large prospective population-based cohort in the northern part of the Netherlands. Lifelines was established as a resource for research on complex interactions between genomic, phenotypic, and environmental factors in the development of chronic diseases and healthy aging. At baseline (2006 – 2013), approximately 167,000 participants completed extensive questionnaires, physical examination, and collection of biomaterials.[18] All participants provided written informed consent before participating in the study. The study has been approved by the Medical Ethical review Committee of the University Medical Center Groningen.

Case definition

For the current cross-sectional analysis, we evaluated adults from whom SAF measurements and glucose values or HbA1c values were available (n=81,286). We have excluded individuals who were pregnant (n=58), who used systemic glucocorticoid therapy (n=345), and who had previously been diagnosed with type 1 (n=182) or type 2 (n=1453) diabetes mellitus. Since SAF measurements may be influenced by the use of skin products,[19] patients who had used sunscreen prior to the SAF measurement were also excluded. Participants were classified as having screen detected diabetes if they had fasting blood glucose ≥7.0 mmol/l, non-fasting blood glucose ≥11.1 mmol/l, or HbA1c ≥6.5%.

Skin autofluorescence

SAF was assessed in a subset of the participants in the Lifelines cohort using the AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands). This non-invasive desktop device uses the characteristic fluorescent properties of certain advanced glycation endproducts (AGEs) to estimate the level of AGE accumulation in the skin. Technical details concerning the optical technique have been extensively described elsewhere.[20]

Questionnaires and physical examination

Extensive baseline questionnaires included questions about demographics, medical history, and medication use. Weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm by trained technicians using calibrated measuring equipment, with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). For the current study, persons were classified as having a history of high blood glucose when they reported previous type 2 diabetes, previous gestational diabetes, or previous diabetes caused by a medical condition.

Finnish diabetes risk score

The original publication of the FINDRISC included two models: the concise and the full model. Since it was reported that the full model improved prediction only minimally, it was decided to use the concise model in this report. The variables in the concise FINDRISC model are: age, BMI, waist circumference, use of anti-hypertensives, and history of high blood glucose.[5]

In the present analysis, multiple imputations by chained equations were applied to eliminate missing values on BMI (0.02%), waist circumference (0.02%), use of anti-hypertensives (1.3%), and history of high blood glucose (0.2%), resulting in five imputed datasets.

Biochemical measures

Blood was collected in the fasting state between 8.00 and 10.00 a.m. and transported to the Lifelines laboratory facility at room temperature or at 4°C, depending on the sample requirements. On the day of collection, HbA1c (EDTA-anticoagulated) was analyzed using a NGSP-certified turbidimetric inhibition immunoassay on a Cobas Integra 800 CTS analyzer (Roche Diagnostics Nederland BV, Almere, the Netherlands). Fasting and non-fasting plasma glucose was measured using a hexokinase method. For the current analysis, blood was collected in a non-fasting state in 1.6% of the participants instead of the fasting state.

Statistical analysis

Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) and R version 3.1.3 (The R Foundation for Statistical Computing). Data are presented as mean ± standard deviation (SD) or as number of participants and percentages. Student's t test or Chi Square test was performed to compare groups. Receiver-operating characteristic (ROC) analysis was used to define groups for SAF in detecting diabetes. Cut-off values were chosen based on 50%, 90% and 97.5% specificity. Logistic regression analysis was executed to determine the association between the FINDRISC variables and diabetes. Furthermore, logistic regression analysis was used to determine score points for SAF in addition to the FINDRISC variables and to determine score points for simplified models. Regression coefficients were multiplied by 4 and rounded off for simplicity allowing comparison of these score values with those of the FINDRISC. Since the five imputed datasets showed comparable regression coefficients and standard errors in the prediction of diabetes, the imputation variation was low. Therefore, we used one randomly chosen imputed dataset for further analysis. Discriminatory ability of the different models was estimated using the area under the ROC curve. Calibration was assessed by Hosmer-Lemeshow chi^2 test by comparing observed and predicted outcomes over deciles of risk.[21] Accurate stratification of individuals into higher and lower risk categories was assessed using risk reclassification analysis in which predicted risk estimates were directly compared to the actual risk observed in each group. The risk groups were defined as: less than 1%, 1% to less than 5%, 5% to less than 10%, and 10% or greater. Furthermore, the net reclassification improvement was calculated according to methods described by Pencina and colleagues[22] with its 95% confidence interval calculated according to methods described by Newcombe.[23]

Results

The demographic and clinical characteristics of the study population are presented in Table 1 for participants with diabetes and participants without diabetes. The prevalence of undiagnosed diabetes was 1.3%. Participants with diabetes were significantly older, had a higher body mass index, a higher waist circumference, and higher SAF values. Also, a higher proportion of participants with diabetes was male, used anti-hypertensives, and had a history of high blood glucose.

Table 1. Characteristics of the study population.

	Diabetes	
Characteristic	**yes (n=1042)**	**no (n=78206)**
Age, *years*	55 ± 12*	44 ± 12
Gender, *male*	561 (53.8)*	32419 (41.5)
Body mass index, *kg/m2*	30.0 ± 5.2*	26.0 ± 4.2
Waist circumference, *cm*		
Female	101 ± 14*	87 ±12
Male	106 ± 13*	95 ± 10
Use of anti-hypertensive drugs, *n (%)*	393 (37.7)*	8450 (10.8)
History of high blood glucose, *n (%)*	12 (1.2)*	172 (0.2)
Skin autofluorescence, *arbitrary unit*	2.30 ± 0.52*	1.90 ± 0.43

*p<0.001 when compared to participants without diabetes.

FINDRISC and SAF in detecting diabetes

Logistic regression analysis showed that all variables of the FINDRISC were significant detectors of diabetes in our study cohort, independent from covariates (Table 2). Furthermore, the addition of SAF (in categories <1.9; 1.9–2.4; 2.4–2.9; ≥2.9 AU) contributed significantly to the model. Subjects in the highest SAF category had a 3.8 times increased risk of having diabetes as compared to subjects in the lowest SAF category. To form the FINDRISC + SAF model, the calculated risk score points for SAF were added to the original risk score points of the FINDRISC. The ROC curve for the FINDRISC model yielded an AUC of 0.802 (95% CI 0.789 – 0.815) for the detection of diabetes. The addition of SAF improved the discriminative value of this model significantly to 0.811 (95%CI 0.798 – 0.824, p<0.001).

Table 2. Multiple logistic regression models for detection of undiagnosed type 2 diabetes in the LifeLines cohort (*n*=79248).

	FINDRISC model			FINDRISC model + skin autofluorescence			Simplified model + skin autofluorescence		
Characteristic	**Regression coefficient**	**OR (95% CI)**	**Score points[1]**	**Regression coefficient**	**OR (95% CI)**	**Score points**	**Regression coefficient**	**OR (95% CI)**	**Score points**
Age, years									
< 45	0	1	0	0	1	0	0	1	0
45-55	0.725	2.06 (1.72 - 2.48)	2	0.541	1.72 (1.42 - 2.07)	2	0.658	1.93 (1.60 – 2.33)	3
55-65	1.349	3.85 (3.18 - 4.67)	3	1.030	2.80 (2.28 - 3.44)	3	1.257	3.52 (2.88 – 4.30)	5
≥ 65	1.757	5.80 (4.72 - 7.12)	4	1.328	3.77 (3.01 - 4.73)	4	1.650	5.21 (4.20 – 6.46)	7
Body mass index,, kg/m2									
< 25	0	1	0	0	1	0	0	1	0
25 – 30	0.581	1.79 (1.44 - 2.22)	1	0.571	1.77 (1.43 - 2.20)	1	0.914	2.49 (2.07 – 3.01)	4
≥ 30	1.464	4.32 (3.39 - 5.51)	3	1.424	4.15 (3.26 - 5.30)	3	2.015	7.50 (6.22 – 9.04)	8
Waist circumference, cm									
♀ < 80, ♂ < 94	0	1	0	0	1	0	-	-	-
♀ 80-88, ♂ 94-102	0.408	1.50 (1.17 - 1.94)	3	0.409	1.51 (1.17 - 1.94)	3	-	-	-
♀ ≥ 88 ♂ ≥ 102	0.716	2.05 (1.58 - 2.65)	4	0.712	2.04 (1.57 - 2.64)	4	-	-	-
Use of anti-hypertensives	0.653	1.92 (1.67 - 2.22)	2	0.602	1.83 (1.58 - 2.11)	2	-	-	-
History of high blood glucose	1.642	5.17 (2.41 - 11.07)	5	1.909	6.75 (3.37 - 13.51)	5	-	-	-
Skin autofluorescence, AU									
< 1.9	-	-	-	0	1	0	0	1	0
1.9 – 2.4	-	-	-	0.490	1.63 (1.38 - 1.93)	2	0.502	1.65 (1.40 – 1.95)	2
2.4 – 2.9	-	-	-	0.653	1.92 (1.57 - 2.36)	3	0.679	1.97 (1.61 – 2.42)	3
≥ 2.9	-	-	-	1.258	3.52 (2.74 - 4.52)	5	1.330	3.78 (2.95 – 4.84)	5

Nagelkerke R^2 is 0.135 for the FINDRISC model, 0.144 for the FINDRISC model + skin autofluorescence, and 0.132 for the simplified model + skin autfluorescence. Model χ^2 is 1409 (p<0.001) for the FINDRISC model, 1505 (p<0.001) for the FINDRISC model + skin autofluorescence, and 1383 (p<0.001) for the simplified model + skin autofluorescence. Hosmer-Lemeshow χ^2 is 16.2 (p=0.024) for the FINDRISC model, 11.7 (p=0.113) for the FINDRISC model + skin autofluorescence, and 16.8 (p=0.019) for the simplified model + skin autofluorescence. [1] score points as published by Lindström et al. (Diabetes Care, 2003); AU, arbitrary unit.

Table 3 shows the number and proportion of participants initially classified by the FINDRISC in 4 risk categories who would be reclassified into higher- or lower-risk categories by the addition of SAF. The proportion of participants reclassified was low (<10%) among those originally classified as having less than 1% or more than 10% risk of diabetes and high (>30%) among the intermediate risk categories. Overall, 15% of all participants were reclassified by the addition of SAF. As shown by the observed diabetes prevalence, most of these participants were reclassified into more accurate risk categories. Reclassification improved by 8.3% among persons who had diabetes and worsened by 0.2% among persons without diabetes, resulting in a net reclassification of 8.0% (95% CI 5.2 – 11.0).

Table 3. Diabetes risk reclassification comparing the FINDRISC model and the FINDRISC model + SAF.

Predicted risk of having diabetes: FINDRISC model	**Predicted risk of having diabetes: FINDRISC + SAF model**				**No. (%) reclassified**
	0-1%	**1-5%**	**5-10%**	**>10%**	
0-1%					4779 (8.9)
Number of participants	48707	4779	0	0	
% classified in each risk stratum	91.1	8.9	-	-	
Observed diabetes prevalence	0.3	1.3	-	-	
1-5%					6727 (30.0)
Number of participants	5537	15673	1015	175	
% classified in each risk stratum	24.7	70.0	4.5	0.8	
Observed diabetes prevalence	1.1	2.7	5.9	9.7	
5-10%					978 (35.3)
Number of participants	0	556	1794	422	
% classified in each risk stratum	-	20	64.7	15.2	
Observed diabetes prevalence	-	5	6.5	9.5	
≥10%					49 (8.3)
Number of participants	0	0	49	541	
% classified in each risk stratum	-	-	8.3	91.7	
Observed diabetes prevalence	-	-	6.1	12.6	

NRI = 0.080 (95% CI 0.052 – 0.110)

Simplified model and SAF in detecting diabetes

ROC curve analysis revealed that the simplified model (age + BMI using the adjusted score points shown in Table 2) had an AUC close to the FINDRISC model (0.795 [95% CI 0.781 – 0.808], p=0.035). The addition of SAF to age + BMI further improved the discriminative value of this model to 0.806 (95% CI 0.793 – 0.818, p<0.001). The AUC of the simplified model + SAF was not significantly different from the FINDRISC model (p=0.365) and the FINDRISC model + SAF (p=0.062). Reclassification of participants due to the addition of SAF to age + BMI is shown in Table 4. Overall, 10% of all participants were reclassified into more accurate risk categories. Reclassification worsened by 0.4% among persons who had diabetes, but improved by 8.2% among persons without diabetes, resulting in a net reclassification of 7.8% (95% CI 5.7 – 9.9).

Table 4. Diabetes risk reclassification comparing age + BMI and age + BMI + SAF.

Predicted risk of having diabetes: age + BMI model	**Predicted risk of having diabetes: age + BMI + SAF model**				**No. (%) reclassified**
	0-1%	**1-5%**	**5-10%**	**>10%**	
0-1%					315 (0.7)
Number of participants	44187	315	0	0	
% classified in each risk stratum	99.3	0.7	-	-	
Observed diabetes prevalence	0.3	1.9	-	-	
1-5%					7355 (22.9)
Number of participants	6912	24780	443	0	
% classified in each risk stratum	21.5	77.1	1.4	-	
Observed diabetes prevalence	0.7	2.5	8.1	-	
5-10%					419 (25.3)
Number of participants	0	294	1239	125	
% classified in each risk stratum	-	17.7	74.7	7.5	
Observed diabetes prevalence	-	3.7	6.5	15.2	
≥10%					72 (7.6)
Number of participants	0	0	72	881	
% classified in each risk stratum	-	-	7.6	92.4	
Observed diabetes prevalence	-	-	6.9	9.9	

NRI = 0.080 (95% CI 0.052 – 0.110)

Prevalence and cut-off points

For the FINDRISC (range 0 – 18 points), the rising prevalence of diabetes with increasing score is shown in Figure 1. Test characteristics of the model are presented in Table 5 for a range of cut-off values. At a score of 7, the sum of sensitivity and specificity was maximised. Of the total population 32% had a score of 7 or higher. This group captures 79% of the cases who have undiagnosed diabetes (sensitivity). Of the persons without diabetes, 68% had a score lower than 7 (specificity).

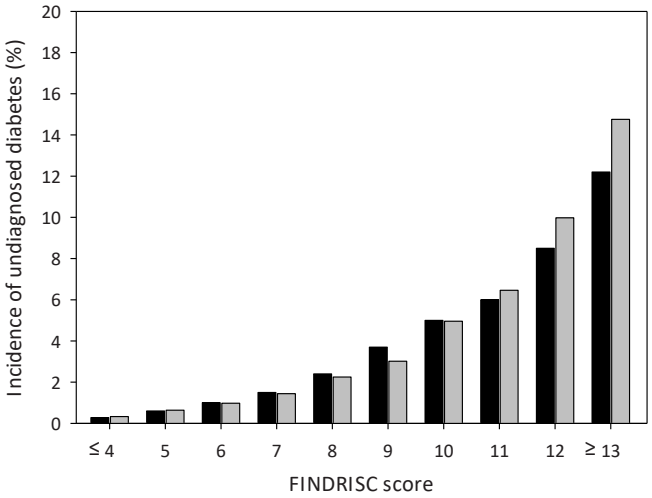

Figure 1. Incidence of undiagnosed diabetes for different scores of the FINDRISC model; black bars, observed risk, grey bars, expected risk.

Table 5. Sensitivity, specificity, and positive and negative predictive value for various cut-off values of the **FINDRISC model** in the detection of undiagnosed diabetes.

Score	Percentage of the population	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
4 or higher	61	93	40	2.0	99.8
5 or higher	51	90	50	2.3	99.7
6 or higher	41	85	60	2.8	99.7
7 or higher	32	79	68	3.2	99.6
8 or higher	18	62	83	4.5	99.4
9 or higher	14	54	87	5.2	99.3
10 or higher	7	35	93	6.6	99.1
11 or higher	4	25	96	7.6	99.0
12 or higher	2	13	99	10.1	98.8

For the FINDRISC model + SAF (range 0 – 21 points), the rising prevalence of diabetes with increasing score is shown in Figure 2. Test characteristics of this model are presented in Table 6 for a range of cut-off values. At a score of 9, the sum of sensitivity and specificity was maximised (sensitivity 75%, specificity 75%).

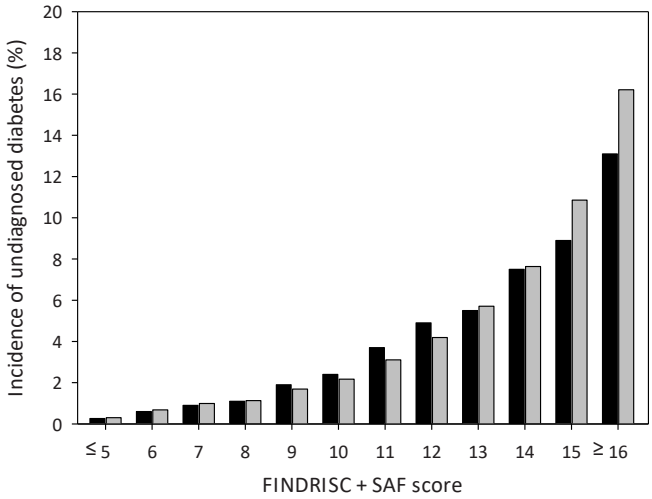

Figure 2. Incidence of undiagnosed diabetes for different scores of the FINDRISC model + SAF; black bars, observed risk, grey bars, expected risk.

Table 6. Sensitivity, specificity, and positive and negative predictive value for various cut-off values of the FINDRISC model + SAF in the detection of undiagnosed diabetes.

Score	Percentage of the population	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
4 or higher	69	96	31	1.8	99.8
5 or higher	59	93	41	2.1	99.8
6 or higher	50	90	51	2.4	99.7
7 or higher	43	87	58	2.7	99.7
8 or higher	32	79	69	3.3	99.6
9 or higher	26	75	75	3.8	99.5
10 or higher	17	62	83	4.7	99.4
11 or higher	13	54	88	5.5	99.3
12 or higher	8	40	92	6.6	99.1
13 or higher	5	29	95	7.6	99.0
14 or higher	3	20	97	9.2	98.9
15 or higher	1	12	99	11.0	98.8

For the simplified model + SAF (range 0 – 20 points), the rising prevalence of diabetes with increasing score is shown in Figure 3. Test characteristics of this model are presented in Table 7 for a range of cut-off values. At a score of 8, the sum of sensitivity and specificity was maximised (sensitivity 83%, specificity 65%). The optimal cut-off points for the FINDRISC, the FINDRISC + SAF, and the simplified model + SAF did not differ between men and women (data not shown).

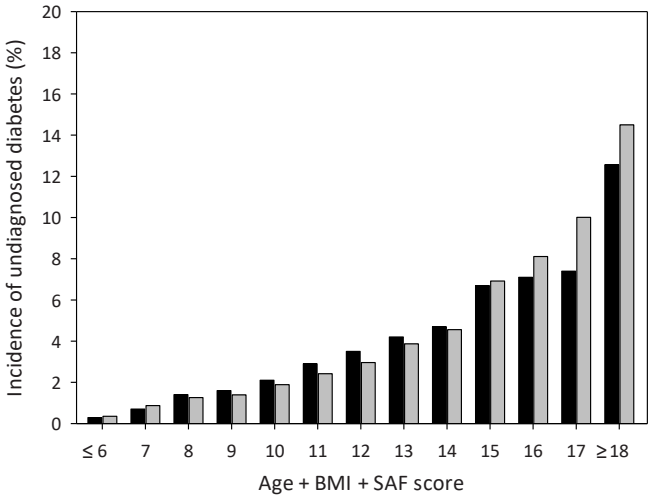

Figure 3. Incidence of undiagnosed diabetes for different scores of the simplified model + SAF; black bars, observed risk, grey bars, expected risk.

Table 7. Sensitivity, specificity, and positive and negative predictive value for various cut-off values of age + BMI + SAF in the detection of undiagnosed diabetes.

Score	Percentage of the population	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
4 or higher	68	95	32	1.8	99.8
5 or higher	56	92	44	2.2	99.8
6 or higher	49	90	51	2.4	99.7
7 or higher	44	88	57	2.6	99.7
8 or higher	36	83	65	3.1	99.7
9 or higher	30	76	71	3.4	99.6
10 or higher	21	67	79	4.1	99.4
11 or higher	17	60	83	4.6	99.4
12 or higher	12	48	89	5.4	99.2
13 or higher	10	43	91	5.7	99.2
14 or higher	6	30	95	6.9	99.0
15 or higher	3	22	97	8.2	98.9
16 or higher	2	16	98	9.0	98.9
17 or higher	1	10	99	10.5	98.8

Discussion

This study shows that SAF improved the performance of the FINDRISC model, an accepted tool for diabetes detection, in a very large and recently recruited population cohort. Furthermore, a simplified model (including age and BMI) with re-estimated score points in combination with SAF was shown to have a similar performance in diabetes detection as the FINDRISC model in combination with SAF.

Discrimination, calibration, and reclassification criteria were used to assess the significance of the addition of SAF as a new biomarker to conventional diabetes risk factors. A significant improvement in discrimination and calibration was shown with the addition of SAF to the FINDRISC model. More importantly, significant reclassification with the addition of SAF was demonstrated, with an overall net reclassification index of 8%. The new model was especially useful in reclassifying participants in intermediate risk categories in which more than 30% of the subjects were reclassified.

Although the calibration of the simplified model with SAF was poor (Hosmer-Lemeshow χ^2 =16.2, p=0.024), the discriminative value was not significantly different from the FINDRISC model combined with SAF. Therefore, the simplified model with SAF may represent an accurate alternative in a setting where answers about medication use and history of high blood glucose seems unreliable or inappropriate. One can think of screening settings not only in medical settings such as general practitioner practices or pharmacies, but also in supermarkets or at big events to reach individuals that avoid or have never been exposed to healthcare. Furthermore, because of its easy and quick performance, the simplified model may improve participation of persons in screening programmes, which is generally low.[24]

Prior studies have addressed the value of skin fluorescence in the detection of diabetes. In subjects at risk for diabetes, skin fluorescence was comparable or superior to HbA1c and fasting plasma glucose for the detection of impaired glucose tolerance and diabetes as detected by the oral glucose tolerance test (OGTT).[15,25] To further improve sensitivity and specificity of diabetes detection, a SAF based decision tree has been developed. It was shown that this decision tree had an equal or superior performance in the detection of diabetes and impaired glucose tolerance in comparison with conventional risk predictors in an intermediate risk group.[16] However, no previous reports showed the validation of skin fluorescence in the detection of diabetes in lower risk groups.

The FINDRISC is often used as a first assessment tool to identify those who may need further glucose testing. It was shown that the optimal cut-off value was a score of ≥7 for the FINDRISC model (sensitivity 79%, specificity 68%), ≥9 for the FINDRISC model plus SAF (sensitivity 75%, specificity 75%), and ≥8 for the simplified model with SAF (sensitivity 83%, specificity 65%). However, since diabetes prevalence was rather low in the Lifelines population, higher cut-off values may be more cost-effective in the Dutch and other populations.[26]

In comparison with the original publication, the area under the receiver operating curve (AUROC) for the FINDRISC was somewhat lower (0.857 vs. 0.802, respectively). It is known that the performance of risk models is generally higher in the population in which they were designed. Furthermore, the present study differs from the Finnish study with respect to population characteristics as well as the way that diabetes was identified. The discriminative performance of the FINDRISC in our cohort was somewhat higher than in other validation studies that addressed the performance of the FINDRISC in the detection of undiagnosed diabetes. In these studies the AUROC ranged from 0.70 to 0.78.[27–32] The difference may be explained by the larger distribution of risk factors in our large cohort study. To illustrate, ROC curve analysis for participants in the age range in which the FINDRISC was originally designed (35-64 years) showed a significantly lower AUC indeed [results not shown].

We have demonstrated that SAF improves the risk classification of individuals at high-risk for diabetes, which opens prospects for, partly already ongoing, studies on related applications. An important opportunity to address is the possible value of SAF alone or in combination with conventional models in the prediction of diabetes. Furthermore, it would be of relevance to investigate whether the addition of SAF to the FINDRISC model would be able to predict cardiovascular complications in diabetes and cardiovascular disease more accurately. The FINDRISC has already been shown to be valuable in the prediction of cardiovascular events in the same population as the FINDRISC was developed[33] and in a randomly selected Finnish population of men aged 45 to 74 years.[34] SAF has already been shown to be valuable in the prediction of cardiovascular events in diabetic populations[14,35] and in patients with peripheral artery disease.[36] Finally, it will be important to confirm validity of the current results in other populations, especially non-Caucasians.

A limitation of our study is the definition of diabetes cases using a single measurement of (fasting) blood glucose and HbA1c, rather than using the repeated measurement required for a clinical diagnosis or using an OGTT. However, the main disadvantage of using the gold standard (OGTT) would be the lower participation rate. Second, history of high blood glucose was not directly addressed in the Lifelines questionnaire. We identified participants with a history of high blood glucose because participants filled in a free space after the question about having diabetes. Therefore, this has probably led to an underestimation of the number of patients with a history of high blood glucose. However, since the prevalence of history of high blood glucose levels was rather low in other Dutch cohorts in which the FINDRISC was validated (0.7 – 1.6%),[37] it is unlikely that this would have changed our main results. Finally, family history of diabetes was incomplete for the Lifelines population, since the corresponding question was later integrated in the baseline questionnaire. Therefore, we were not able to compare the performance of the FINDRISC (+ SAF) to the updated Finnish diabetes risk score[38] and other existing risk scores.[39–41]

In conclusion, the combination of the simple to perform FINDRISC score, plus the easy, non-invasive SAF measurement provides a clinical tool for diabetes detection. The new model is especially useful in reclassifying participants in intermediate risk categories in which further blood glucose testing should confirm the presence of diabetes. Furthermore, a simplified model with age, BMI, and SAF may represent an accurate alternative in a setting where answers about medication use and history of high blood glucose seems unreliable or inappropriate. The resulting early identification of patients with diabetes may be able to prevent or delay micro- and macrovascular complications.

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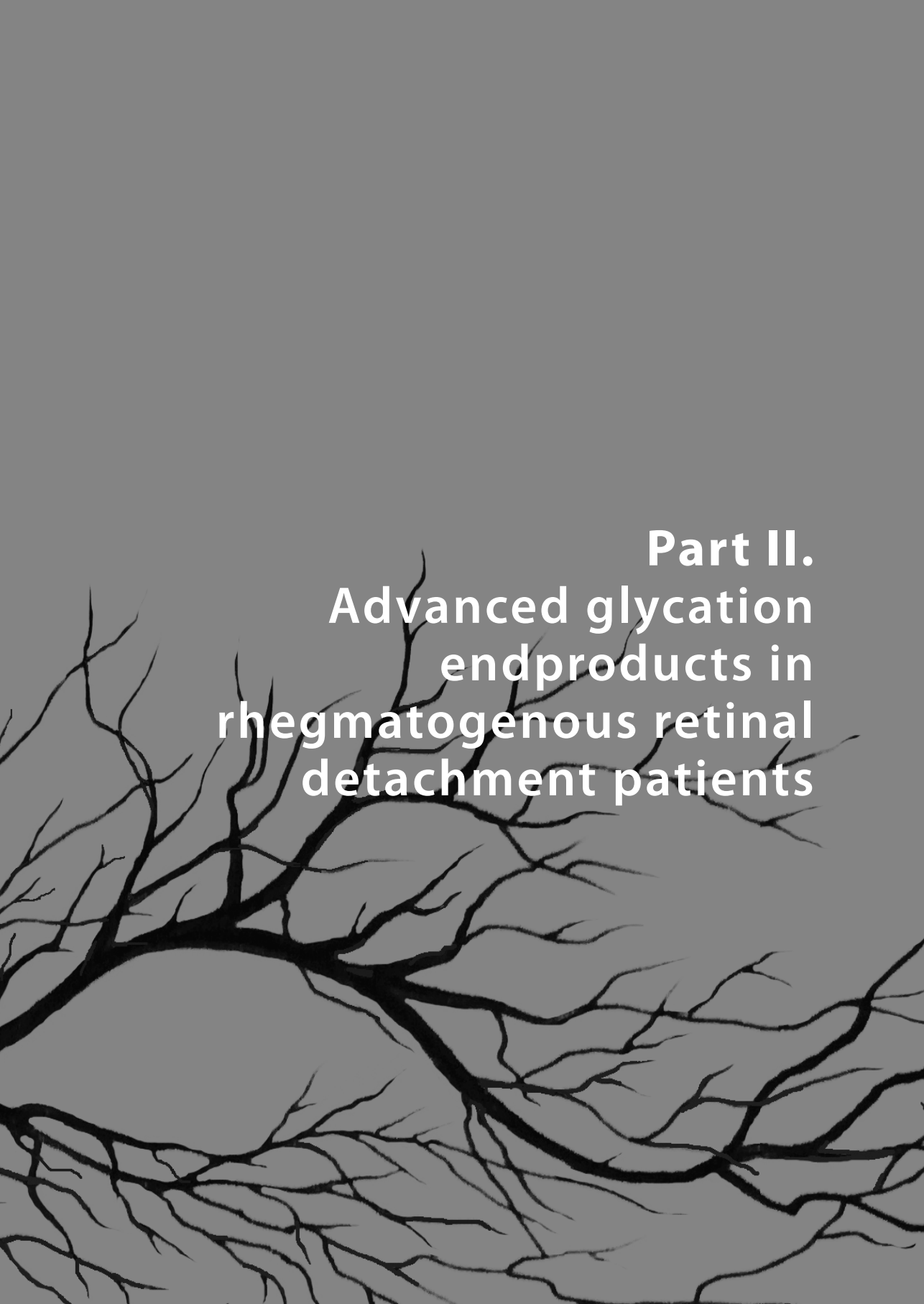

Part II. Advanced glycation endproducts in rhegmatogenous retinal detachment patients