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Evaluation of the German Diabetes Risk Score as a screening tool for undiagnosed diabetes

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Abbreviations

ADA	American diabetes association
ALT	Alanine aminotransferase
AUC	Area under the receiver operating characteristic curve
Cambridge DRS	Cambridge diabetes risk score
CAPI	Computer assisted personal interview
CI	Confidence interval
CVD	Cardiovascular disease
DISHES	Dietary Interview Software for Health Examination Studies
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
FINDRISK	Finish diabetes risk score
FPG	Fasting plasma glucose
German DRS	German Diabetes Risk Score
GGT	γ-glutamyltransferase
GNHIES	German National Health Interview and Examination Survey
HbA1c	Glycosylated haemoglobin
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IRIS II	International randomized trial of Interferon/Ara-C versus ST1571
KORA	Cooperative Health Research in the Region of Augsburg
MeSyBePo study	Metabolic Syndrome Berlin Potsdam study
OGTT	Oral glucose tolerance test
PROCAM	Prospective Cardiovascular Münster
ROC curve	Receiver operating characteristic curve
TÜF	Tübingen Family Study for Type 2 Diabetes
WHO	World Health Organisation

Abstract

Background Regional German studies estimated the prevalence of undiagnosed diabetes to be almost as high as the prevalence of diagnosed diabetes. Even before symptoms of diabetes occur, diabetes related secondary diseases can be developing and cause increased health care expenditures. The German Diabetes Association recommends the application of the German Diabetes Risk Score (German DRS) to screen for undiagnosed diabetes and thus enable early treatment of diabetic individuals.

Methods Data from the representative German National Health Interview and Examination Survey 1998 (N=7124), including a sample of the residential population aged 18-79 years, was used to compute the German DRS. Participants with prevalent diabetes or missing data were excluded from analyses (N=718). Correlation between score and biomarkers related to type 2 diabetes was assessed by Pearson's correlation coefficients. Sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC) were calculated for both undiagnosed diabetes (glycosylated haemoglobin (HbA1c) ≥6.5%; fasting plasma glucose (FPG) ≥126 mg/dl) and intermediate hyperglycaemia (HbA1c: 5.7-6.4%; FPG: 100-125 mg/dl).

Results Among the 6406 subjects, on average women had a lower score value than men. The German DRS was significantly negatively correlated with HDL-cholesterol among both genders while it was significantly positively correlated with glucose, HbA1c, triglycerides, total cholesterol, γ-glutamyltransferase, and alanintransferase. Sensitivity and specificity for undiagnosed diabetes at a cut point of ≥500 was 93.9/50.4 using FPG and 91.2/56.6 using HbA1c as diagnostic criterion. For intermediate hyperglycaemia it was 70.9/63.0 applying FPG and 67.3/67.2 applying HbA1c for diagnosis. The estimated AUC for undiagnosed diabetes was 0.79 using FPG and 0.84 using HbA1c. AUC values for intermediate hyperglycaemia were 0.72 applying FPG and 0.74 using HbA1c.

Conclusion Compared to two other German study populations, the German DRS yielded similar discriminatory ability for undiagnosed diabetes among an 18-79 years old German survey population. Further research with regard to identification of high risk groups for diabetes and to differences in performance of the German DRS between both genders and different age-groups would be useful to improve efficiency of the German DRS as a screening tool for undiagnosed diabetes.

1. Introduction

1.1 Background

Diabetes mellitus is a chronic metabolic disease caused by either insufficient pancreatic insulin secretion, deficient insulin action in the body, or a combination of both. Diabetes leads to hyperglycaemia and can cause several long-term complications, e.g. retinopathy possibly leading to blindness, nephropathy possibly leading to renal failure, or peripheral neuropathy increasing the risk of amputations (1, 2). About 346 million people all over the world already suffer from diabetes (3). However, following a worldwide trend the prevalence of diabetes among the Germany population is expected to further increase within the next years, causing rising health care expenditures and decreasing quality of life (4-6).

The health care burden of diabetes could possibly be decreased by lifestyle interventions aiming to prevent development of diabetes and by early treatment of those who already suffer from diabetes (7-11). Thus, it is important to identify people at increased risk for developing future diabetes and to detect those suffering from undiagnosed diabetes at an early stage (11). For these reasons, several diabetes risk scores based on a variety of risk factors have been developed in different countries (10, 12-17). However, the German Diabetes Association recommends the application of the German Diabetes Risk Score (German DRS) to screen for undiagnosed diabetes among the German population (1).

1.2 Objectives

The intentions of the present study were

- To compute the German DRS for participants of the German National Health Interview and Examination Survey 1998 (GNHIES).
- To analyse the distribution of the German DRS among the survey population.
- To examine correlations between biomarkers related to pathophysiology of type 2 diabetes and the computed German DRS.
- To examine the performance of the German DRS when used as a screening tool for undiagnosed diabetes and intermediate hyperglycaemia among the survey population.

1.3 Overview of diabetes mellitus

Diabetes mellitus is one of the leading causes of premature death worldwide along with other non-communicable diseases, e.g. cardiovascular diseases (CVD) and cancer (18). Three major forms of diabetes mellitus have been defined. First, type 1 diabetes mellitus, which is caused by autoimmune destruction of the pancreatic ß-cells resulting in a lack of insulin production. Type 1 diabetes accounts for about 5-10% of all diabetic cases and is not preventable according to present understanding (1-3). Second, type 2 diabetes mellitus, which is thought to be caused by an interaction of several factors, e.g. genetic predisposition, overweight, sedentary lifestyle. Therefore, to a large part it is regarded as being preventable (3, 11, 19). Patients suffering from type 2 diabetes usually show insulin resistance and relative insulin deficiency to some degree (1, 2, 6). Type 2 diabetes mellitus accounts for approximately 80-90% of all diabetic cases in adults (6). Finally, the third type, gestational diabetes is characterized by hyperglycaemia, which occurs first during pregnancy but does usually not persist after delivery (1, 2). Other types of diabetes are associated, for example, with genetic defects of the pancreatic ß-cells, diseases of the exocrine pancreas, or infections. However, their prevalence among the German population is rather low (1, 2).

In Germany, about 9% of all adults suffered from diagnosed diabetes mellitus accounting for approximately six million prevalent cases in 2009. The prevalence of diabetes rises with increasing age and decreasing socio-economic status (5, 6, 20). Compared to 2002/03, the prevalence of diagnosed diabetes has increased in Germany and is expected to further grow due to demographic changes and changes of lifestyle (5, 21-23). However, also improved diagnostic measures might add to an increase in prevalence of diagnosed diabetes (24).

Diabetes mellitus has severe effects on the body and elevates the risk of suffering from, e.g. CVD, kidney failure, blindness, neuropathy, and limb amputation (3, 11, 19). Therefore, it decreases life expectancy, increases costs for medical care, and diminishes ability to work (6, 25). In Germany, diabetes and its complications and subsequent diseases led to increased direct health care costs of approximately € 19 billion in 2007, when compared to non-diabetic patients (1.8 times higher costs) (5, 24). Costs indirectly connected with diabetes through diminished working ability and early retirements further increase health care expenditures (5, 20, 26).

Studies have shown that a considerably large part of the worldwide population also suffers from undiagnosed diabetes (27). However, currently representative data about the prevalence of undiagnosed diabetes among the German population are not available (6). Though, regionally confined data indicate that the prevalence of undiagnosed diabetes is about as high as the prevalence of diagnosed diabetes among a study population from Southern Germany (28, 29). Due to lacking clinical symptoms of the disease at early stages, the diagnosis of type 2 diabetes usually occurs several years after its onset (11). However, even before symptoms of diabetes are shown, the risk of developing diabetes related secondary diseases is already increased. Treatment of these secondary diseases is approximately three times more expensive than the health care costs caused by treating diabetes itself (26). Consequently, early detection of individuals suffering from undiagnosed diabetes and those being at increased risk of developing type 2 diabetes might help to decrease total health care expenditures and improve overall wellbeing (3, 11, 24, 26).

1.4 Overview of different diabetes risk scores developed or applied in Germany

Several diabetes risk scores or risk models have been developed in different countries intended to identify individuals at high risk of developing diabetes and those suffering from undiagnosed diabetes, respectively (10, 12-17). The following paragraph presents and compares diabetes risk scores/models which have either been developed or applied in Germany or both. As shown in table 1, in Germany four different diabetes risk scores/models have been developed (German DRS, IRIS II (International randomized trial of Interferon/Ara-C versus ST1571) score, KORA (Cooperative Health Research in the Region of Augsburg) type 2 diabetes prediction models, PROCAM (Prospective Cardiovascular Münster) multiple logistic function model) (10, 30-32). Besides, six diabetes risk scores either originated in foreign countries (Cambridge DRS, FINDRISK (Finish Diabetes Risk Score), Framingham Simple Clinical Model, Predictive Clinical Model (San Antonio Heart Study), Rotterdam Diabetes Questionnaire) or in Germany (German DRS) have been applied in further German study populations (33) (10, 34-40). Moreover, two scores developed in Germany (KORA type 2 diabetes prediction model, PROCAM multiple logistic function model) have been externally validated in the Netherlands and in China, respectively (41, 42). Finally, two risk scores, one developed in Finland (FINDRISK) and one in Germany (German DRS), have been modified in different ways, e.g. shortened, extended, and/or changed in the included variables (35-37, 43, 44).

Table 1. Diabetes risk scores and risk models developed and/or applied in Germany.

Name of original risk score (original AUC)	First author (year)	Study design (study population) and purpose	Sample size and age	Considered risk factors	Sensitivity/ specificity in % (cut point)	AUC
Cambridge DRS (AUC=0.80 for undiagnosed diabetes) (14)	Rathmann (2005) (33)	CSS (KORA) Application, CS validation Screening for undiagnosed diabetes	N = 1,353 Age: 55-74y	Age (continuous), sex, BMI (categorical), use of antihypertensives, steroid use, parental history of diabetes[1], smoking (current and former)	58/69 (score >0.199)	0.67 (for undiagnosed diabetes, based on FPG ≥126 mg/dl or 2h PG ≥200 mg/dl)
FINDRISK (AUC=0.80 for undiagnosed diabetes; AUC=0.85 for prediction of high risk for diabetes) (12)	Rathmann (2005) (33)	CSS (KORA) Application, CS validation Screening for undiagnosed diabetes	N = 1,353 Age: 55-74y	Categorical variables: age, BMI, WC, use of antihypertensives, PA, daily consumption of vegetables, fruits or berries[2]	82/43 (score ≥9)	0.65 (for undiagnosed diabetes, based on FPG ≥126 mg/dl or 2h PG ≥200 mg/dl)
	Scherbaum (2006) (34)	CSS Efficiency of FINDRISK as screening tool for undiagnosed diabetes on population level	N = 58,254 Age ≥55 y	Age, BMI, WC, use of antihypertensives, history of high blood glucose, PA, daily consumption of vegetables, fruits or berries, family history of diabetes[3]	NS Higher score → higher risk of IFG, IGT or T2DM	NS FINDRISK not efficient as screening tool on population level
	Bergmann (2007) (35)	Cohort study (3 years follow-up) Validation Screening for undiagnosed diabetes (C1, baseline) Prediction of high risk for diabetes (C2 und C3)	N = 526 (increased T2DM risk[4]) Age:41–79 y 3 conditions: C1: identification of asymptomatic T2DM C2: prediction of T2DM risk with intervention C3: prediction of T2DM risk without intervention	Shortened, modified German FINDRISK version (categorical variables): age, BMI, WC, use of antihypertensives, history of high blood glucose, family history of diabetes[3,5]	C1: 71/63 (score≥9) C2: 63/83 (score≥11) C3: 74/67 (score≥9)	C1: 0.75 (for undiagnosed diabetes, based on 2h PG ≥200 mg/dl) C2: 0.79 (for prediction of high diabetes risk, based on see C1) C3: 0.78 (for prediction of high diabetes risk, based on see C1)
	Schwarz (2009) (37)	CSS ability of FINDRISK to identify insulin resistance (IR); CS validation of results	CSS: N = 771 (family history of MS) Age: 14-93y CS validation: N = 526 (increased T2DM risk[4]) Age: 41–79 y	Shortened, modified German FINDRISK version (categorical variables): age, BMI, WC, use of antihypertensives, history of high blood glucose, family history of diabetes[3,5]	CSS: 77.5/67.9 (score ≥12) Validation: 72.1/68.2 (score ≥9)	CSS: 0.78 (for IR, based on HOMA-IR >5) Validation: 0.74 (for IR, based on HOMA-IR >5)

	Li (2009) (36)	CSS Validation; development of a simplified alternative model Screening for undiagnosed diabetes	N = 771 (family history of MS) Age:14-93y	Shortened, modified German FINDRISK version (categorical variables): age, BMI, WC, use of antihypertensives, history of high blood glucose, family history of diabetes[3,5] Simplified version (SV) (continuous variables): age, BMI, history of high blood glucose Simplified version (SV) (categorical variables): age, BMI, history of high blood glucose	German FINDRISK 70/79 (score ≥14) SV (cont.): 85/79 SV (cat.): 79/80 (score ≥8)	German FINDRISK 0.81 (for undiagnosed diabetes, based on 2h PG ≥200 mg/dl) SV (cont.): 0.88 (for undiagnosed diabetes, based on 2h PG ≥200 mg/dl) SV (cat.): 0.86 (for undiagnosed diabetes, based on see SV cont.)
Framingham simple clinical model (AUC=0.85 for prediction of high risk for diabetes) (16)	Li (2007) (38)	Cohort study Validation Prediction of high risk for diabetes	N = 465 Middle aged adults (Ø age: 54 y)	Categorical variables: age, sex, family history of diabetes (1st & 2nd-degree), BMI, BP, HDL cholesterol, triglycerides, fasting plasma glucose levels	NS	0.86 (for prediction of high diabetes risk, based on 2h PG ≥200 mg/dl)
German diabetes risk score (GDRS) – classic version	Schulze (2007) (10)	Cohort study (EPIC Potsdam) Development of score Prediction of high risk for diabetes	N = 25,167 Age: ♀ 35-65y ♂ 40-65 y	Full model (continuous variables): age, WC, height, history of hypertension, PA, smoking (current and former), consumption of red meat, whole-grain bread, coffee, and alcohol	83/68 (score ≥500) 68/81 (score ≥550) 50/90 (score ≥600)	0.84 (for prediction of high diabetes risk, based on self-report of diagnosis, medication or dietary treatment, verified by physician)
	Schulze (2007) (10)	Cohort study (EPIC Heidelberg) Validation Prediction of high risk for diabetes	N = 23,398 Age: 35-65 y	Full model	94/67 (score ≥ 500) 80/79 (score ≥ 550)	0.82 (for prediction of high diabetes risk, based on self-report, reviewing medical records and death certificates)
	Schulze (2007) (10)	CSS (MeSyBePo) Validation Screening for undiagnosed diabetes	N = 1,011	Full model (dietary information missing in most participants)	94/43 (score ≥ 500) 83/57 (score ≥ 550)	0.75 (for undiagnosed diabetes, based on 2h PG ≥200 mg/dl)

	Schulze (2007) (10) Schulze (2008) (40)	CSS (TÜF) Validation Screening for undiagnosed diabetes CSS (EPIC Potsdam) CS validation, screening for IFG	N = 686 Age: Ø 37 y N = 2,223 (640 fasting blood samples) Age: Ø ♀ 48 y Ø ♂ 52 y	Full model (dietary information missing in most participants) Full model	83/72 (score ≥ 500) 62/83 (score ≥ 550) 74/71 (score ≥ 500)	0.83 (for undiagnosed diabetes, based on 2h PG ≥200 mg/dl) 0.79 (for IFG, based on FPG 100-125 mg/dl; n = 640)
GDRS – simplified version	Schulze (2007) (43)	Cohort study (EPIC Potsdam) Development of score; prediction of high risk for diabetes	N = 25,167 Age: ♀ 35-65 y ♂ 40-65 y	Full model using categorical variables	83/69 (score ≥40)	0.83 (for prediction of high diabetes risk, based on see classic version)
GDRS – extended version	Schulze (2009) (44)	Cohort study (EPIC Potsdam) Development of score Prediction of high risk for diabetes	N = 1,962 plus 579 incident cases Ø age cohort: 49 y Ø age cases: 55 y	Full model plus fasting glucose, HbA1c, triglycerides, HDL cholesterol, γ-glutamyltransferase, alanine aminotransferase	NS	0.90 (for prediction of high diabetes risk, based on see classic version)
IRIS II score	Forst (2004) (30)	CSS (IRIS II) Development of score Screening for IR in diabetic patients	N = 4,265 diabetic patients (without insulin therapy) Ø age: 64 y	Categorical variables: BMI, fasting blood glucose, fasting triglycerides, fasting HDL cholesterol (number of points for each factor depends on BP)	34/95 (score ≥70; indicating IR= HOMA-IR >2)	NS
KORA S4/F4 type 2 diabetes prediction models	Rathmann (2010) (31)	Cohort study (KORA S4/F4) (7 year follow-up Development of score Prediction of high risk for diabetes	N = 887 Age: 55-74y	Model 1 (M1): age, sex, BMI, parental diabetes, smoking (current and former), hypertension Model 2 (M2): M1 + fasting glucose, HbA1c, uric acid Model 3 (M3): M2 + 2-h glucose	69/74 (score ≥0.117) 82/73 (score ≥ 0.087) 81/84 (score ≥0.127)	0.76 (for prediction of high diabetes risk based on validated physician diagnosis/FPG ≥126 mg/dl/2h PG ≥200 mg/dl) 0.84 (for prediction of high diabetes risk based on see M1) 0.89 (for prediction of high diabetes risk based on see M1)

	Abbasi (2012) (41)	Cohort study (PREVEND, Netherlands) (7.7 years follow-up) Validation Prediction of high risk for diabetes	Sample 1: N = 2,050 Age ≥ 55 y Sample 2: N = 6,317 (total population) Age:28-75 y	M1 M2 = M1 + fasting glucose[5] M3 = M2 + uric acid[5]	NS	Sample 1: M1= 0.66 M2 & M3 = 0.81 (for prediction of high diabetes risk based on FPG ≥126 mg/dl or random plasma glucose ≥200 mg/dl or self-report of physician diagnosis or pharmacy registered use of antidiabetics) Sample 2: M1= 0.77 M2 & M3 = 0.85 (for prediction of high diabetes risk based on see sample 1)
Predictive clinical model (San Antonio Heart study) (AUC=0.84 for prediction of high risk for diabetes) (15)	Rathmann (2005) (33)	CSS (KORA) Application, CS validation Screening for undiagnosed diabetes	N = 1,353 Age: 55-74y	Continuous variables: age, sex, systolic BP, BMI, HDL cholesterol, parental history of diabetes[2], fasting plasma glucose level (original factor ethnicity was not used in validation study)	78/85 (score >0.100; cutpoint chosen with similar specificity to fasting glucose alone)	0.90 (for undiagnosed diabetes based on FPG ≥126 mg/dl or 2h PG ≥200 mg/dl → not sig. different from FPG level alone 0.89)
PROCAM multiple logistic function model	Von Eckardstein (2000) (32)	Cohort study (PROCAM) (6.3 years follow-up) Development of risk model Prediction of high risk for diabetes	N = 3,737 men Age: 36-60 y	Age, BMI, fasting glucose, HDL cholesterol, family history of diabetes, hypertension	70/80 57/90 (with specificity defined)	0.79 (for prediction of high diabetes risk based on self-reported diagnosis or FPG ≥126 mg/dl; no improvement compared to only fasting glucose)
	Chien (2008) (42)	Cohort study (Chin-Shan) (10 year follow-up) Validation Prediction of high risk for diabetes	N = 2,960 Age: ≥ 35 y	Age, BMI, fasting glucose, HDL cholesterol, family history of diabetes, hypertension	66/56 (score ≥ -14.4)	0.63 (for prediction of high diabetes risk based on FPG ≥126 m/dl or intake of antidiabetics)

Rotterdam diabetes study questionnaire (AUC=0.68 for undiagnosed diabetes) (13)	Rathmann (2005) (33)	CSS (KORA) Application, CS validation Screening for undiagnosed diabetes	N = 1,353 Age: 55-74y	Basic predictive model (categorical variables): age, sex, BMI, use of antihypertensives	74/39 (score >6)	0.61 (for undiagnosed diabetes based on FPG ≥126 mg/dl or 2h PG ≥200 mg/dl)

[1] = originally also history of diabetes in siblings was used, but this information was not available for the KORA sample (33)
[2] = history of high blood glucose levels was used in original score, but not in validation study (12, 33)
[3] = family history of T2DM was not included in original FINDRISK score, but the authors suggest to further include this risk factor in the score (suggestion: 5 score points for first degree family history and 3 score points for second degree family history) (12)
[4] = due to family history of T2DM, obesity, or dyslipoproteinemia (35)
[5] = questions about dietary habits and PA did not add much predictive power (35)
[6] = model 2 and model 3 differ from the original KORA models (33, 41)

AUC= area under the receiver operating characteristic curve (ROC curve) (discriminatory ability); **Sensitivity** (true-positive probability) = is the probability of identifying any person suffering from the disease (diabetes) with the help of the used score (45); **Specificity** (true-negative probability) = is the probability of identifying any person not suffering from the disease (diabetes) with the help of the used score (45); **PG** = post-load glucose level; **IFG** (impaired fasting glucose) = 100 – 125 mg/dl (2); **IGT** (impaired glucose tolerance) =2-h value in oral glucose tolerance test 140 – 199 mg/dl (2); **MS** = metabolic syndrome; **WC** = waist circumference; **PA** = physical activity; **BP** = blood pressure; **BMI** = Body Mass Index (kg/m²); **T2DM** = type 2 diabetes mellitus; **CS** = cross-sectional; **CSS** = cross-sectional study; **HOMA-IR** = homeostasis model assessment of insulin resistance; **IR** = insulin resistance;
KORA = Cooperative Health Research in the Region of Augsburg;
FINDRISK = Finish Diabetes Risk Score;
EPIC = European Prospective Investigation into Cancer and Nutrition;
MeSyBePo = Metabolic Syndrome Berlin Potsdam Study;
TÜF = Tübingen Family Study for Type 2 Diabetes;
PROCAM = Prospective Cardiovascular Münster;
IRIS = International Randomized trial of Interferon/Ara-C versus ST1571;
PREVEND = Prevention of renal and vascular end stage disease

Compared to original studies, in confirmative studies, most risk scores show a lower ability to discriminate between prevalent undiagnosed diabetic cases and non-diabetic individuals and between individuals at high risk for diabetes and low risk for diabetes. Exceptions are, the predictive clinical model (San Antonio Heart Study), the Framingham simple clinical model, and the KORA S4/F4 type 2 diabetes prediction model. One of the reasons for this result is the fact that original study populations and populations of validation studies usually differ in their characteristics. A decreased accuracy (discriminatory ability) is reflected by a smaller area under the receiver operating characteristic (AUC) curve than in an original study. A ROC curve is created by plotting the sensitivity (true-positive probability) against the false-positive probability (1-specificity) of each possible cut-off point of a chosen prediction model. The AUC values range from 0.5 to 1.0, 0.5 indicates a non-informative test result and 1.0 a perfect prediction (accuracy) of the model (44, 46). Especially, when the risk score has been developed in a foreign country its detected accuracy in the validation study shrinks (10, 12, 13, 15, 16, 33, 38, 41, 42). This is one of the reasons, why it is recommended to validate the performance of the risk score within the target population before implementing it as a screening tool, for example (33, 47). Based on the same reason Herman at al. recommend, to

rather implement a risk score as screening tool that has been developed in the same population (48).

Altogether, five diabetes risk scores/risk prediction models used only non-invasive measures (Cambridge DRS, FINDRISK, German DRS, KORA S4/F4 type 2 diabetes prediction model 1, Rotterdam diabetes study questionnaire) (10, 12-14, 31). Inclusion of biochemical markers led to an improvement in the accuracy and in the prediction of an increased risk for type 2 diabetes in the KORA type 2 diabetes prediction model and the German DRS (31, 44). However, inclusion of genetic markers did not further improve prediction of type 2 diabetes risk in the German DRS (44). The application of the predictive clinical model of the San Antonio Heart Study and the extended version of the German DRS yielded the highest AUCs (0.90). Both used non-invasive and invasive measures e.g. HDL-cholesterol and fasting glucose level (15, 44). Among the risk scores solely based on non-invasive measures, the simplified alternative version of the FINDRISK score (categorical model: AUC=0.86; continuous model: AUC=0.88) and the classic version of the German DRS (AUC=0.83) showed the highest discriminatory ability for undiagnosed diabetes (10, 36).

As mentioned before, the aim of diabetes risk scores is either to screen for undiagnosed diabetes or to predict the individual risk of developing diabetes. The German DRS has been developed based on a prospective cohort study and is therefore able to identify individuals at high risk for diabetes. In two validation studies it has been demonstrated that it also shows high discriminatory ability with regard to screening for undiagnosed diabetes (10, 39). On the other hand, since it is based on cross-sectional data, the simplified FINDRISK version is only intended to be used to screen for undiagnosed cases of diabetes (36). As a screening tool it is an advantage to use non-invasive measures only as it is less costly (49). Besides, it is less time consuming and more convenient for the participants compared to, e.g. an oral glucose tolerance test (OGTT) or other invasive measures. A screening tool based on non-invasive measures might thus lead to a higher compliance among participants (15, 50).

Both, German DRS and simplified FINDRISK version have been developed based on German study populations and show a high discriminatory ability (AUC value) (10, 36, 39). Nevertheless, the German DRS seems to have the best applicability as a screening instrument among the German population. First of all, the German DRS is based on a large cohort population and has been validated in three other German study populations, showing high

accuracy for prediction of increased risk for future diabetes and for detection of undiagnosed diabetes (10). In contrast, the development of the FINDRISK score was based on a Finish study population and the simplified FINDRISK version was based on a relatively small sample without being validated yet (12, 36). Moreover, the study population used to develop the simplified FINDRISK version was at increased risk for developing the metabolic syndrome and is therefore not generalizable to the common German population (36). Indeed, also a modified German version of FINDRISK has been developed (51). However, it has only been validated in one cross-sectional and one cohort study with both rather small sample sizes. Nevertheless, it yielded only slightly lower accuracy for prediction of increased risk for diabetes and similar accuracy for detection of undiagnosed diabetes compared to the German DRS (35, 36). Though, the high detected accuracy can possibly be explained by the fact that the variable "history of high blood glucose" is used in all FINDRISK versions. It includes the prediabetic states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) but also diabetes itself, which obviously is strongly related to the identification of "undiagnosed diabetes" (39). Other risk scores developed in Germany, like the PROCAM multiple logistic function model and the KORA S4/F4 type 2 diabetes prediction model, have not been validated in German study populations yet and were based on smaller sample sizes. Besides, all other scores using only non-invasive measures yielded lower AUC values and/or were validated in a lower number of studies (see table 1). In summary, the German DRS shows a high accuracy for undiagnosed diabetes, it is based on a large German cohort study, it has been validated in three other studies, and it only uses non-invasive measures. Therefore, the German DRS is used as a screening instrument in a representative sample of the German population in the present investigation.

2. Methods

2.1 German National Health Interview and Examination Survey 1998

For the purpose of the following analyses, data from the cross-sectional GNHIES conducted from October 1997 until March 1999 was used. The survey consists of a representative sample of the residential German population and comprises 7124 subjects aged between 18 and 79 years including 3450 men and 3674 women. A two-stage stratified and clustered sampling technique was used. First, a representative sample of 130 communities or community districts (sampling points) distributed all over Germany was randomly chosen, stratified for federal state and community size. Among these sample points 80 were located in

western Germany and 40 in eastern Germany. Second, in each of the chosen sampling points the local population registry was used to randomly select residents with regard to gender and age. The overall response rate of the GNHIES was 61.4%. To ensure statistically sound results regarding analysis of differences between eastern and western Germany a disproportionally higher number of participants was chosen from eastern Germany. For all analyses of the data a weighting factor was used to adjust for variations between characteristics of the selected participants and demographic characteristics of the residential German population. This step improves representativeness of the sample. The described procedure guarantees a representative sample of the German population (52, 53).

The GNHIES consists of a core survey and five more specific modules (environmental survey, nutrition survey, folate study, mental health survey, and pharmaceutical survey) (54). For the present analyses, information from the core survey and the nutrition survey were used. The core survey included all 7124 participants and encompassed a self-administered questionnaire about health status, socio-economic status, living conditions, nutritional behaviour (FFQ), smoking, and physical activity, a medical and anthropometric examination, a computer assisted personal interview (CAPI) by a medical doctor about the participant's medical history and drug intake, and laboratory diagnostics of blood and urine samples (54). In the nutrition survey the usual dietary intake of the past four weeks was assessed for a subsample of 4030 participants. For that purpose, a personal interview was performed by qualified nutritionists using DISHES (Dietary Interview Software for Health Examination Studies), which is a dietary assessment software based on the dietary history method. DISHES was validated against a 3 day weighted dietary record and a 24 hour dietary recall. Pearson's correlation coefficients for macronutrients ranged between 0.34 and 0.69 for the 3 day weighted record. The correlation between DISHES and the 24 hour dietary recall for macronutrients ranged between 0.27 and 0.65 (55).

2.2 Subjects

After exclusion of subjects already suffering from diagnosed diabetes reported in the medical interview (N = 369), subjects who reported to use blood sugar medication (N = 10), and subjects with missing information about any of the variables used to calculate the German DRS (N = 339), a total of 6406 subjects remained for further analyses.

2.3 German Diabetes Risk Score

The German DRS was developed using a subsample of the EPIC (European Prospective Investigation into Cancer and Nutrition) Potsdam cohort study (N = 25,167, age = 35-65 years). It was validated against data from three other German studies (EPIC-Heidelberg, Tübingen Family Study for Type 2 Diabetes (TÜF), Metabolic Syndrome Berlin Potsdam (MeSyBePo) study). The German DRS is intended to be used to calculate the individual five year probability of developing type 2 diabetes mellitus. For example, a score < 423 points is equivalent to a possibility of less than 1% for developing diabetes in the following 5 years, whereas ≥ 658 points are equivalent to a probability of more than 10%. The risk score is supposed to be used to identify persons at high risk of developing diabetes. It can further be used to identify individuals with undiagnosed diabetes (10, 39). For the calculation of the original German DRS, only variables measured non-invasively and being significantly associated with diabetes risk were included (10). The German DRS is computed by the following equation (10, 44):

> German DRS = 7.4 x waist (cm) – 2.4 x height (cm) + 4.3 x age (years) + 46 x history of hypertension (self-reported) + 49 x red meat (each 150 g/day) – 9 x whole-grain bread (each 50 g/day) – 4 x coffee (each 150 g/day) – 20 x moderate alcohol (between 10 and 40 g/day) – 2 x physical activity (h/week) + 24 x former smoker + 64 x current heavy smoker (≥ 20 cigarettes/day)

All multipliers are based on the calculated ß-coefficients in the original Cox regression model. The probability of developing diabetes in the following five years is calculated by (10):

$$p\,(\text{diabetes}) = 0.999854^{\exp(\text{score points}/100)}$$

2.4 Definition and assessment of variables

For calculation of the German DRS for GNHIES participants all variables shown in table 2 were used.

Table 2. Comparison between variables used from EPIC-Potsdam and those used from the GNHIES to compute the German DRS.

Variable	German DRS/EPIC-Potsdam	German DRS/GNHIES
Waist circumference	Anthropometric measurements (cm) - performed by interviewers trained in anthropometric measurement - measured accurately to the next 0.5 cm	Anthropometric measurements (cm) - performed by trained health professionals - measured accurately to the next 0.5 cm
Height	Anthropometric measurements (cm) - performed by interviewers trained in anthropometric measurement - measured accurately to the next 0.1 cm	Anthropometric measurements (cm) - performed by trained health professionals - measured accurately to the next 0.1 cm
Age	Standardised self-administered questionnaire - years	Standardised self-administered questionnaire - years
History of hypertension	Standardised personal interview - performed by a trained physician - self-reported (yes/no)	CAPI - performed by a trained physician - self-reported (yes/no)
Red meat intake	Semiquantitative FFQ - asking for frequencies and amounts of intake of different kinds of red meat - categories from “never” to “five times/day or more” - estimation of portion size by using photographs of standard portion sizes - g/day	FFQ (core survey) - asking for frequencies of overall meat intake (including poultry) - categories from “(almost) never” to “several times per day” DISHES (subsample, specific module) - Estimated average intake (g/d) for each frequency category (FFQ) based on data of the German Nutrition Survey (dietary history method)
Whole-grain bread intake	Semiquantitative FFQ - Asking for frequencies and amounts of intake of whole grain bread and rolls - categories from “never” to “five times/day or more” - estimation of portion size by using photographs of standard portion sizes - g/day	FFQ (core survey) - asking for frequencies of consumption of whole grain bread and rolls - categories from “(almost) never” to “several times per day” DISHES (subsample, specific module) - Estimated average intake (g/d) for each frequency category (FFQ) based on data of the German Nutrition Survey (dietary history method)
Coffee intake	Semiquantitative FFQ - Asking for frequencies and amount of intake of coffee with caffeine - categories from “never” to “five times/day or more” - estimation of portion size by using photographs of standard portion sizes - g/day	FFQ (core survey) - Asking for frequencies of coffee consumption with caffeine - categories from “(almost) never” to “several times per day” DISHES (subsample, specific module) - Estimated average intake (g/d) for each frequency category (FFQ) based on data of the German Nutrition Survey (dietary history method)

Alcohol consumption	Semiquantitative FFQ - Asking for frequencies, type of beverage and amount - categories from “never” to “five times/day or more” - type of beverages (beer, wine, fruit wine, sparkling wine, distilled spirits) - estimation of portion size by using photographs of standard portion sizes (glasses or bottles) - calculation of alcohol intake (ethanol in g/d) based on the German Food Code and Nutrient Data Base version II.3 (56)	Semiquantitative FFQ (core survey) - asking for frequencies, type of beverage and amount - categories from “(almost) never” to “several times per day” - type of beverage (beer, wine, fruit wine, sparkling wine, distilled spirits) - estimation of portion size by asking for litre amounts or glasses (2 cl) consumed - calculation of alcohol intake (g/d) based on standard content of ethanol of 4.8 vol. % for beer, 11 vol. % for wine, 33 vol. % for spirits (57)
Physical activity (PA)	Standardised PA questionnaire - separately for summer and winter - average time (hours) spent/week during 1 year - assessment of sport activities, biking, and gardening	Standardised self-administered questionnaire - average time (hours) spent for sport activities per week - five categories from “no sport” to “regularly more than 4 hours per week”
Smoking	Standardised personal interview - former smoking for at least 3 months (yes/no/do not know) - current smoking (yes/no/do not know) - current smoking (number of cigarettes/day)	Standardised self-administered questionnaire - current and former smoking (never, current (daily), current (occasionally), former (stopped more than 1 year ago), former (stopped in the past 12 months)) - current smoking (number of cigarettes/day)

References: (10, 58, 59)

Table 2 illustrates that there were no major differences in assessment of waist circumference, height, age, history of hypertension, alcohol consumption and smoking behaviour between EPIC-Potsdam and GNHIES. However, there were differences in the way of examining red meat, whole-grain bread and coffee intake. While for EPIC-Potsdam it was measured by a semiquantitative FFQ asking for frequencies and amounts, the FFQ of the GNHIES’ core survey only asked for frequencies of consumption. Thus, the average amount consumed by each frequency group (core survey) was estimated by using data from a survey module with a subsample of 4030 participants (nutrition survey). Based on dietary history interviews (DISHES) the typical frequencies and amounts of food intake within the last four weeks were acquired (55) and used to calculate the average amounts consumed per day. By combining information from the core survey (frequencies) and the nutrition survey (amounts) the average amount consumed per day for each food frequency category was estimated. This estimation was only based on the subsample of 4030 participants, who took part in both the core survey and the nutrition survey. Daily intake of meat, coffee and whole grain bread was not normally distributed. Therefore, individual average intake was estimated by using the median intake. Furthermore, whereas the food groups “coffee”, and “whole grain bread” were similar in both

studies, the GNHIES asks for overall meat consumption without differing between red meat and poultry. Finally, there are also differences in the examination of physical activity. While EPIC-Potsdam asks specifically for the amount of hours spent per week for biking, gardening and sport activities, the GNHIES examines overall physical activity in five categories ranging from “no physical activity at all” up to “regularly, more than 4 hours per week” (10). For calculating the German DRS the weekly time spent with physical activity was estimated by the middle time of each category band, e.g. for less than one hour a time of 0.5 hours was assigned, and between one and two hours a time of 1.5 hours was allocated.

2.5 Assessment and selection of biomarkers of type 2 diabetes

The correlation between the derived German DRS and the following biochemical markers for type 2 diabetes was assessed:

> whole blood HbA1c, serum glucose, serum HDL cholesterol, total serum cholesterol, serum triglycerides, serum alanine aminotransferase and serum γ-glutamyltransferase.

The gel monovette system provided by Becton-Dickinson (Franklin Lakes, NJ, USA) was used for taking venous blood samples after a minimum fasting period of 3-hours. All blood samples were processed and distributed into aliquots immediately after they were taken. Serum samples were instantly stored at -40 °C until biochemical analyses were carried out (60).

Glycosylated haemoglobin (HbA1c) was analysed in whole blood by using a test-kit of Recipe and a HPLC on a Diamat HPLC analyser (both Bio-Rad, Munich, Germany) (60). HbA1c reflects the individual’s average blood glucose levels of the past two till three months and can further be used for metabolic control of the diabetic patient and prediction of diabetes related complications (61). HbA1c was approved as diagnostic criterion for diabetes by the WHO only recently in 2011 (62). According to the American Diabetes Association (ADA), for the current investigation a level of HbA1c $\geq$ 6.5% was used to diagnose diabetes and an HbA1c level between 5.7 and 6.4% was used to identify individuals at increased risk for developing diabetes (intermediate hyperglycaemia) (2).

All other metabolic markers were measured in serum. Glucose was measured by glucose oxidase-peroxidase-4-aminophenazone method (Merck, Darmstad, Germany) (60). The concentration of fasting plasma glucose (FPG) is one of the classical measures for diagnosing diabetes mellitus besides plasma glucose 2 hours after an OGTT. According to ADA, in the

present investigation a cut point for FPG[1] of ≥ 126 mg/dl was used to diagnose diabetes. Impaired fasting glucose (IFG) as a measure for intermediate hyperglycaemia was defined by a FPG level of 100 till 125 mg/dl according to ADA[2] (2). All serum glucose levels were converted into plasma glucose levels by using the following equation: *venous plasma (mmol/l) = -0.137 + 1.047 x venous serum (mmol/l)* (63).

HDL-cholesterol was examined by using an immunoseparation-based homogeneous assay (WAKO, Chuo-ku, Osaka, Japan) while total cholesterol was measured with the enzymatic cholesterol oxidase-peroxidase-4-aminophenazone method (Merck). Triglycerides were assessed with glycerophosphate oxidase-peroxidase-4-aminophenazone method (Merck) (60). Triglycerides, HDL-and total cholesterol are metabolic markers of the fat metabolism. Increased levels of fasting triglycerides (> 150mg/dl), and decreased levels of HDL-cholesterol (men: < 40 mg/dl, women: < 54 mg/dl), respectively, are associated with an increased CVD risk but also with insulin resistance, IFG and IGT (16, 61, 64-67). Furthermore, increased overall cholesterol levels (> 200 mg/dl) are related to hyperglycaemia (66).

Alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) are both liver-enzymes and markers for liver function (61, 68, 69). Moreover, GGT is possibly a marker for oxidative stress (70). Increased levels of GGT (e.g. in serum > 28 U/l for men and > 18 U/l for women (61) and/or ALT (e.g. in serum > 22U/l for men and > 17 U/l in women(61) are also associated with increased levels of liver fat and an increased risk of developing diabetes and IGT (67-69, 71). For measuring GGT the colorimetric Granutest 100 (Merck) was used to conduct a kinetically colour test according to Szasz at 25°C. ALT was assessed by using MPR3 (Roche).

2.6 Statistical analyses

For all statistical analyses the statistical analysis system (SAS version 9.2, SAS Institute, Inc., Cary; NC, USA) was used. Statistical significance was assumed for $p < 0.05$. For all analyses a weighting factor was used to ensure statistical representativity. The weighting factor takes differences between the survey population and the German population in 1998, with regard to

[1] After a fasting period of at least 8 hours (2).

[2] Another criterion for measuring increased risk for diabetes is impaired glucose tolerance (IGT) which is defined by 2-hour plasma glucose levels between 140 and 199 mg/dl after a 75g OGTT (2).

age, sex, federal state, and community size, into account (52). Significant differences between both genders concerning all score criteria and biomarkers (not normally distributed, Kolmogorov-Smirnov test, $p>0.01$) were examined using Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. A histogram showing the distribution of the German DRS among both men and women was prepared by creating score subgroups and calculating the proportion (%) of participants in each of the defined groups.

All biomarkers were logarithmically transformed before correlation analyses to reach an approximately normal distribution. Correlation between German DRS and the selected log-transformed biomarkers was calculated by using Pearson's correlation coefficient.

The performance of the German DRS was assessed by computing sensitivity and specificity. Sensitivity (true positive rate) was defined by the proportion of participants whose score values were above the cut offs of 300, 400, 500, 600, 700, and 800 respectively among all participants who suffered from undiagnosed diabetes using FPG $\geq$ 126 mg/dl and HbA1c $\geq$ 6.5% as diagnostic criterion. Specificity (true negative rate) was defined by the proportion of participants whose score values were below the cut offs of 300, 400, 500, 600, 700, and 800 respectively among those participants who do not suffer from undiagnosed diabetes (FPG < 126 mg/dl, HbA1c < 6.5%) (2, 15). In addition, sensitivity and specificity to identify an increased risk for diabetes (FPG 100-125 mg/dl, HbA1c 5.7-6.4%) were assessed by using the same cut offs (2). Moreover, the AUC-ROC curve was computed. The AUC value is used to predict the accuracy of the German DRS to discriminate between diabetic and non-diabetic cases and between persons at increased risk for diabetes and with non-increased risk, respectively (72).

Besides, all analyses were performed with a subsample excluding pregnant women (N = 15) and with a subsample based on the age-groups of the EPIC-Potsdam study population (women: 35-65 years, men: 40-65 years). Finally, sensitivity, specificity and the AUC values of the computed German DRS were calculated stratified by gender.

3. Results

3.1 Descriptive statistics

The whole study population comprised 6406 participants, including 3142 men and 3264 women. Table 3 shows that women are significantly older and shorter than men. Moreover, their waist circumference is significantly smaller than the waist circumference of men. On

average men are significantly more physically active, and consume significantly more meat per day whereas women have a significantly higher mean daily intake of whole grain bread. A significantly higher proportion of men consume a moderate amount of alcohol per day compared to women. There are no significant differences in the average amount of coffee consumed per day and in the proportion of participants suffering from hypertension between both genders. A significantly higher percentage of men are former smokers or current heavy smokers compared to women. Besides, men show a significantly higher mean German DRS value than women and a higher probability of developing diabetes in the next five years. The range of the German DRS was 144.97 – 1083.12 for men and 139.18 – 908.71 for women.

Table 3. Characteristics among men (N = 3142) and women (N = 3264) of the study population.

	Men N = 3142	**Women N = 3264**	**P value**
Component of the German DRS			
Age (years)	44.14 (43.54 – 44.74)	46.07 (45.41 – 46-72)	0.0111
Waist circumference (cm)	96.07 (95.64 – 96.49)	84.12 (83.66 – 84.58)	< 0.0001
Height (cm)	176.41 (176.14 – 176.69)	163.54 (163.29 – 163.80)	< 0.0001
Physical activity (h/week)	1.22 (1.17 – 1.28)	0.95 (0.90 – 1.00)	< 0.0001
Moderate alcohol consumption (10-40 g/day) (%)	34.20 %	11.05 %	< 0.0001
Hypertension (%)	19.79 %	21.78 %	0.2723
Meat consumption (portions [each 150g]/day)	0.63 (0.62 – 0.63)	0.56 (0.56 – 0.57)	< 0.0001
Whole grain bread consumption (slices [each 50g]/day)	0.62 (0.59 – 0.64)	0.81 (0.78 – 0.83)	< 0.0001
Coffee consumption (cups [each 150g]/day)	2.16 (2.11 – 2.12)	2.15 (2.09 – 2.20)	0.7938
Former smoker (%)	27.65 %	15.54 %	< 0.0001
Current heavy smoking (%) ≥20 cigarettes/day	17.31 %	8.78 %	< 0.0001
DRS points	511.36 (505.90 – 516.82)	455.11 (449.23 – 461.00)	< 0.0001
Probability of developing diabetes (%)	5.74 % (5.39 – 6.08)	4.18 % (3.88 – 4.48)	< 0.0001
Biomarker of type 2 diabetes			
Glucose (mg/dl)	98.64 (98.07 – 99.21)	95.50 (94.96 – 96.05)	< 0.0001
HbA1c (%)	5.48 (5.45 – 5.50)	5.40 (5.38 – 5.42)	< 0.0001
HDL-cholesterol (mg/dl)	47.93 (47.39 – 48.47)	62.58 (61.91 – 63.26)	< 0.0001
Triglyceride (mg/dl)	144.09 (140.80 – 147.47)	103.25 (101.26 – 105.27)	< 0.0001
Cholesterol (mg/dl)	225.88 (224.04 – 227.74)	228.03 (226.19 – 229.88)	0.6340
γ-glutamyltransferase (GGT) (U/l)	17.66 (17.26 – 18.07)	11.42 (11.17 – 11.67)	< 0.0001
Alanin aminotransferase (ALT) (U/l)	14.99 (14.72 – 15.27)	9.84 (9.68 – 10.00)	< 0.0001

Values are given as weighted arithmetic mean (95% CI) or weighted percentage for all Diabetes-Risk Score components and as weighted geometric means (95% CI) for all logarithmically transformed biomarkers.

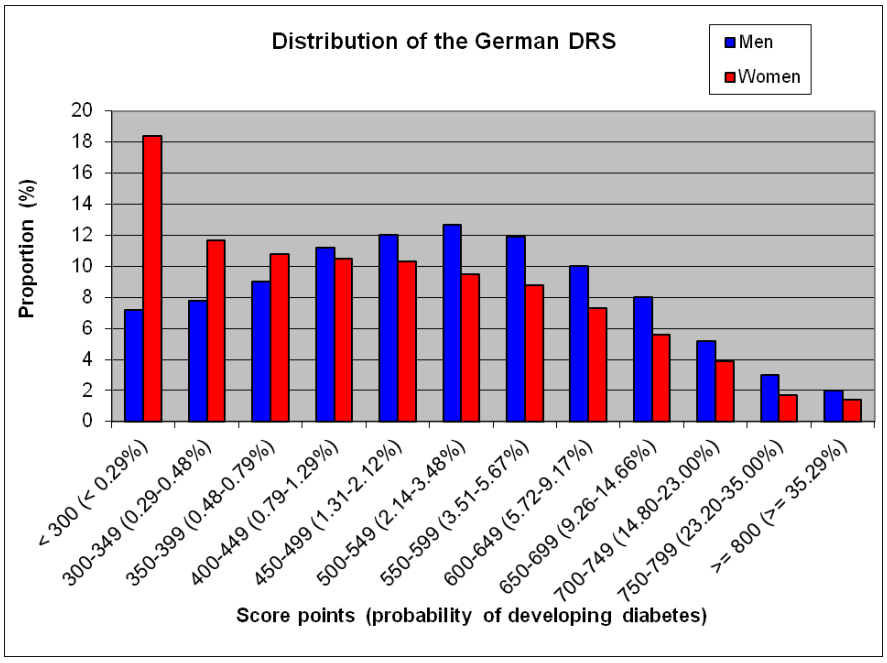
Mean fasting glucose was 101.64 mg/dl (CI: 99.91 mg/dl – 103.41 mg/dl) for men (N=400) and 96.47 mg/dl (CI: 95.12 mg/dl – 97.83 mg/dl) for women (N=660) (p-value: < 0.0001). Mean fasting triglycerides were 118.31 mg/dl (CI: 111.39 mg/dl – 125.66 mg/dl) for men (N=400) and 95.94 mg/dl (92.20 mg/dl – 99.82 mg/dl) for women (N=660) (p-value: < 0.0001).

Considering the levels of biomarkers for type 2 diabetes, men had a significantly lower HDL-cholesterol level than women. Women had significantly lower levels of glucose, HbA1c, triglycerides, GGT, ALT. The level of total cholesterol did not differ significantly between both men and women.

3.2 Distribution of the score

A higher proportion of women has a low diabetes risk score and thus a lower probability of developing diabetes compared to men (figure 1). Especially for a score below 300 points the proportion of women is more than twice as high as the proportion of men. A higher proportion of men show a high diabetes risk score[3] and thus a higher probability of developing diabetes compared to women. The distribution of the German DRS among men is similar to a normal curve whereas the score decreases steadily among women.

Figure 1. Distribution of the German DRS and the probability of developing diabetes among men (N = 3142) and women (N = 3264) among a German study population.



3.3 Correlation between German Diabetes Risk Score and different biomarkers of type 2 diabetes

The computed German DRS was significantly positively correlated with glucose, HbA1c, triglycerides, overall cholesterol, GGT, and ALT among both men and women (table 4). Among both genders it was significantly negatively correlated with HDL-cholesterol.

[3] ≥ 500 points according to Schulze et al. (43).

Correlation coefficients for all biomarkers were higher among women than among men. Among a subsample of men (N = 400) and women (N = 660) who fasted overnight, glucose was significantly positively correlated ($p < 0.0001$) with the German DRS (correlation coefficient: men: 0.35; women: 0.45). Besides, there was a significant ($p < 0.0001$) positive correlation between triglycerides and the German DRS among both genders (correlation coefficient: men: 0.43; women: 0.45).

Table 4. Pearson correlation among men (N = 3142) and women (N = 3264) between German DRS and biomarkers of type 2 diabetes.

Biomarker	Men N = 3142	Women N = 3264
Glucose (mg/dl)	0.30	0.40
HbA1c (%)	0.37	0.54
HDL-cholesterol (mg/dl)	- 0.14	- 0.16
Triglyceride (mg/dl)	0.35	0.47
Cholesterol (mg/dl)	0.42	0.46
γ-glutamyltransferase (GGT) (U/l)	0.33	0.39
Alanintransferase (ALT) (U/l)	0.20	0.37

All biomarkers were logarithmically transformed. All correlation coefficients were significant at a level of $p < 0.0001$.

3.4 Performance of the German Diabetes Risk Score

Sensitivity[4] and specificity[5] of the German DRS to identify cases with undiagnosed diabetes are illustrated in table 5 and 6. While in table 5 FPG was used to detect undiagnosed diabetes, in table 6 HbA1c was used for diagnosis. For both diagnostic measures sensitivity is decreasing with rising score values while specificity is increasing at the same time.

Sensitivity and specificity of the German DRS to identify intermediate hyperglycaemia, was calculated at different cut points and by using either FPG or HbA1c as diagnostic criterion. The German DRS yielded lower sensitivity but higher specificity in identifying intermediate hyperglycaemia compared to identifying undiagnosed diabetes for each of the chosen cut points and for both diagnostic criteria (table 7 and 8).

[4] Probability of a diseased subject being detected as diseased at a certain cut-off (45,46).

[5] Probability of a non-diseased subject being detected as non-diseased at a certain cut-off (45,46).

Table 5. Sensitivity and specificity of the German DRS to identify undiagnosed diabetes at different cut points based on FPG ≥ 126 mg/dl (N = 1060).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	49	100.0	889	87.9	12.1
≥ 400	49	100.0	712	70.4	29.6
≥ 500	46	93.9	501	49.6	50.4
≥ 600	31	63.3	302	29.9	70.1
≥ 700	19	38.8	116	11.5	88.5
≥ 800	8	16.3	21	2.1	97.9

FPR = false-positive rate (100-specificity)

Table 6. Sensitivity and specificity of the German DRS to identify undiagnosed diabetes at different cut points based on HbA1c ≥ 6.5 % (N = 6032).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	238	99.6	4992	86.2	13.8
≥ 400	235	98.3	3820	65.9	34.1
≥ 500	218	91.2	2515	43.4	56.6
≥ 600	172	72.0	1256	21.7	78.3
≥ 700	93	38.9	406	7.0	93.0
≥ 800	23	9.6	63	1.1	98.9

FPR = false-positive rate (100-specificity)

Table 7. Sensitivity and specificity of the German DRS to identify intermediate hyperglycaemia at different cut points based on FPG 100 – 125 mg/dl (N = 1060).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	360	96.3	529	83.0	17.0
≥ 400	330	88.2	382	60.0	40.0
≥ 500	265	70.9	236	37.0	63.0
≥ 600	179	47.9	123	19.3	80.7
≥ 700	73	19.5	43	6.8	93.2
≥ 800	15	4.0	6	0.9	99.1

FPR = false-positive rate (100-specificity)

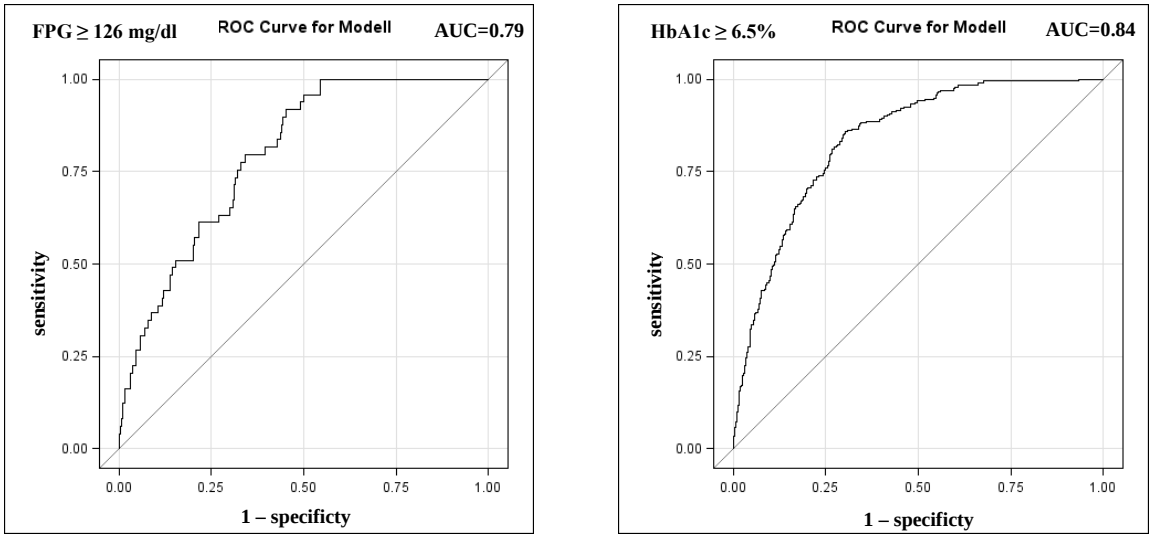
Table 8. Sensitivity and specificity of the German DRS to identify intermediate hyperglycaemia at different cut points based on HbA1c 5.7 – 6.4 % (N = 6032).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	1686	95.8	3306	82.0	18.0
≥ 400	1520	86.4	2300	57.0	43.0
≥ 500	1192	67.7	1323	32.8	67.2
≥ 600	693	39.4	563	14.0	86.0
≥ 700	256	14.5	150	3.7	96.3
≥ 800	47	2.7	16	0.4	99.6

FPR = false-positive rate (100-specificity)

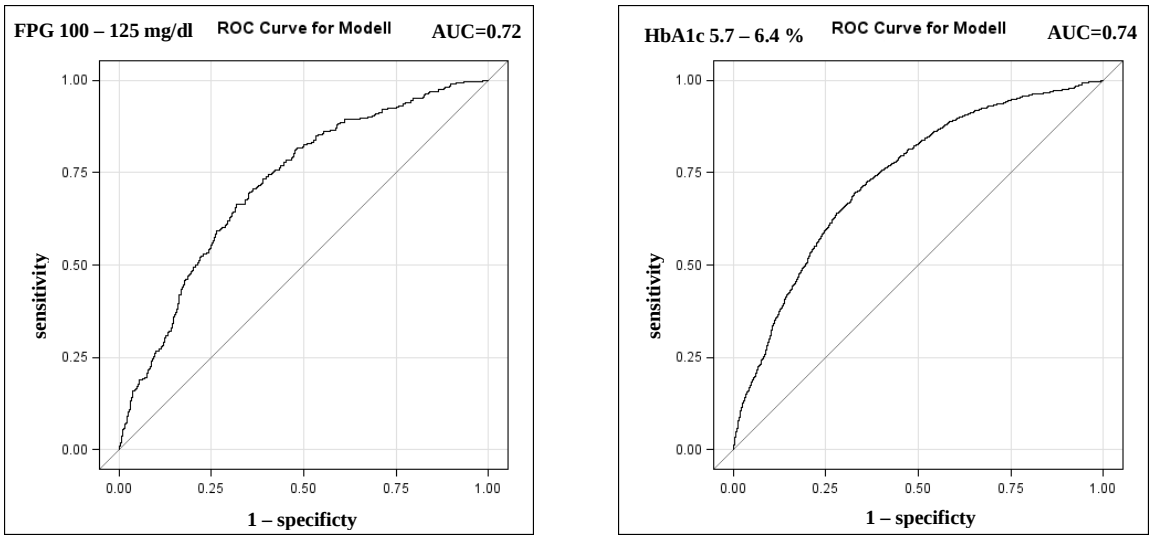
The accuracy of the German DRS for the prediction of undiagnosed diabetes was measured by using the American Diabetes Association's (ADA) diagnostic criterion of FPG ≥126 mg/dl. In a further step, it was measured by using the diagnostic criterion of HbA1c ≥ 6.5%. For detection of intermediate hyperglycaemia, a range for FPG of 100-125 mg/dl and a range for HbA1c of 5.7-6.4% both according to ADA were used (2). The AUC for prediction of undiagnosed diabetes was 0.79 when using FPG and 0.84 when using HbA1c as diagnostic criterion (presented in figure 2).

Figure 2. ROC curve of the German DRS for prediction of undiagnosed diabetes using FPG ≥126 mg/dl (N = 1060) and using HbA1c ≥6.5% (N = 6032).



The results for the prediction of intermediate hyperglycaemia are presented in figure 3. The AUC value based on FPG was 0.72 while the AUC value based on HbA1c was 0.74.

Figure 3. ROC curve of the German DRS for prediction of intermediate hyperglycaemia using FPG 100-125 mg/dl (N = 1060) and using HbA1c 5.7-6.4% (N = 6032).



3.5 Sensitivity analyses

Analysing the performance of the German DRS stratified by gender (see appendix 1) yielded an about 2 times higher specificity among women than among men for the cut offs of ≥300 and ≥400. These results were valid for both undiagnosed diabetes and intermediate hyperglycaemia and for both FPG and HbA1c as diagnostic criterion. When FPG was used as diagnostic criterion, sensitivity for undiagnosed diabetes was at least 1.5 times higher among women than among men above the cut offs of 700 and 800 points. Based on FPG, sensitivity for intermediate hyperglycaemia was at least 2 times higher among men above the cut offs of 700 and 800 points. The AUC values among women were higher than those calculated for men. For example, the AUC value for undiagnosed diabetes based on FPG was 0.87 among women and 0.67 among men, based on HbA1c it was 0.86 among women and 0.82 among men.

Statistical analyses based on a subsample, taking only the age-group of the EPIC-Potsdam study into account[6] (appendix 2), led to similar results for the descriptive statistics while the distribution of the calculated German DRS among women changed. On average women were still more likely than men to have a lower score value, but the distribution among women was closer to a normal distribution, though, still slightly skewed to the left. All biomarkers for

[6] women: 35-65 years, men: 40-65 years

type 2 diabetes were significantly correlated with the computed German DRS. Correlation coefficients were lower for most biomarkers than among the complete survey population except for triglycerides and ALT among women. There were no major differences in sensitivity and specificity between the diagnostic criteria FPG and HbA1c for both undiagnosed diabetes and intermediate hyperglycaemia. The calculated AUC values for the subsample where lower compared to the complete sample.

All statistical analysis were performed on a subsample excluding all pregnant women (N = 15). The results were very similar to the results of the whole sample and were not reported.

4. Discussion

The aim of the present investigation was to examine the distribution of the computed German DRS, to scrutinize its correlation with biomarkers related to type 2 diabetes, and to analyse its performance as a screening tool.

4.1 Results

Distribution of the score

On average, men reach a higher German DRS than women and consequently also have a higher probability of developing type 2 diabetes in the following 5 years. In one of their studies, Schulze *et al.* found a similar result with men on average yielding higher German DRS values than women (40). Other studies found a higher risk of developing diabetes among men than among women as well (20, 31, 35, 67). However, the prevalence of diagnosed diabetes was higher among German women than among German men in 2009 (6). These findings suggest that there might be a higher number of men suffering from undiagnosed diabetes, whereas diabetes among women is more often diagnosed.

Moreover, also the distribution of the score among women and men differed. While on average women were more likely to achieve a lower score, especially lower than 300 points (distribution skewed to the left), men on average were more likely to yield a higher score (≥500 points) (normal distribution). Analyses of the score distribution in a subsample including only the age-groups of the EPIC-Potsdam study, i.e. women aged 35-65 years and men aged 40-65 years, showed a decreased proportion of women with a mean score lower than 300 points. In a further step, the score distribution among women younger than 35 years,

men younger than 40 years, and women and men older than 65 years was analysed. Differences in the distribution among the examined age-groups indicate, that young women are responsible for the high proportion of low average score values in the female survey population. On the contrary, the average score value increases among both middle aged and elderly women and men, reflecting the increasing prevalence of diabetes with rising age (20). The positive association between age and the risk of developing diabetes is further reflected by its consideration in the equation of the German DRS (10). Furthermore, among all age-groups on average women achieve lower score values than men exhibiting the decreased risk for diabetes among women (20). However, the distribution of the score among women aged 35-65 years is more similar to the score distribution of men aged 40-65 years than the score distribution of women and men among the whole survey population. This finding suggests that the risk of diabetes is more similar among women and men aged 35-65 years than among women and men aged 18-79 years.

A less healthy lifestyle contributed more to a high risk of diabetes among men than among women. For example, in the present study population on average men show a significantly higher consumption of red meat, a lower consumption of whole grain bread, and a higher proportion of heavy smokers and former smokers compared to women. All of these factors are positively associated with high risk of diabetes (10). In addition, on average men also have a significantly higher waist circumference than women, which is also positively associated with diabetes risk (10). On the other hand, in the present study on average men are significantly younger, taller, and more physically active than women. Besides, a higher proportion of men consume moderate amounts of alcohol per day compared to women. All of which are factors negatively associated with diabetes risk (10). These findings indicate that among the present survey population the differences in score values and thus in diabetes risk among both genders are related to differences in nutritional behaviour (red meat and whole grain bread intake), the high proportion of male heavy and former smokers, and a higher waist circumference among men.

Association with biomarkers related to type 2 diabetes

The higher average score value among men is accompanied by a significantly lower mean HDL-cholesterol level and significantly higher average levels of glucose, HbA1c, triglycerides, GGT, and ALT compared to women. Similar results have been found in other

studies. For example, Schulze *et al.* found higher levels of glucose, GGT, and triglycerides and also lower levels of HDL-cholesterol among men (40). In addition, Nannipieri *et al.* detected higher ALT and GGT levels among men than among women (69). Increased levels of plasma glucose, HbA1c, triglycerides, GGT, and ALT and decreased levels of HDL-cholesterol are associated with a higher prevalence of diabetes and with increased risk for diabetes (2, 62, 65, 66, 69). Consequently, the biomarker profile of men reflects their higher German DRS and further explains their higher risk of diabetes.

Among both men and women the calculated German DRS was significantly positively correlated with glucose, HbA1c, total cholesterol, triglycerides, GGT, and ALT. In addition, it was significantly negatively associated with HDL-cholesterol. The correlation coefficients were higher for fasting glucose and fasting triglycerides compared to the non-fasting coefficients. The current findings are comparable to the results of Schulze *et al.*, who also found significant positive correlations between German DRS and glucose, HbA1c, triglycerides, and GGT and a significant negative correlation between score and HDL-cholesterol among both genders (40). Generally, correlation coefficients were similar in the present investigation and the study of Schulze *et al*. Although, the correlation coefficients with glucose and HbA1c in the current study were at least 1.5 times higher among both genders than those found by Schulze *et al.* On the other hand, the correlation coefficient with HDL-cholesterol was almost 2 times higher among women and about 1.5 times higher among men in the study of Schulze *et al.* compared to the current investigation. In both studies, women showed higher correlation coefficients than men, except for glucose in the study of Schulze *et al.* (40). An association between prevalent diabetes and different biomarkers, and intermediate hyperglycaemia and different biomarkers, respectively, was found in other studies as well. For example, for HDL-cholesterol, total cholesterol, triglycerides, ALT, and GGT (20, 66, 67, 69). Finally, the present investigation was able to detect correlations between the German DRS and all of the studied biomarkers of type 2 diabetes.

Performance of the German DRS

Based on data of a German study population, the German DRS yielded a sensitivity/specificity of 93.9/50.4 for undiagnosed diabetes based on FPG and 91.2/56.6 for undiagnosed diabetes based on HbA1c (cut off ≥500). These results are comparable to the findings in the MeSyBePo study. Here, for the same cut off, the German DRS yielded a

sensitivity/specificity of 94/43% based on FPG. However, in the TÜF study it yielded lower sensitivity, but higher specificity (83/72%) based on FPG (10). Other diabetes risk scores assessed in Germany yielded lower sensitivity combined with higher specificity and in some cases also a lower specificity (33, 35, 36). Nevertheless, sensitivity and specificity always depend on the chosen cut-off (15), therefore it might be difficult to compare results of different studies using different cut points.

In the present investigation, the accuracy of the German DRS for detection of undiagnosed diabetes was 0.79 based on FPG and 0.84 based on HbA1c. Consequently, the accuracy of the German DRS based on FPG was higher than in the MeSyBePo study (AUC=0.75) but lower than in the TÜF study (AUC=0.83) (10). Moreover, compared to most other studies, where diabetes risk scores have been applied to a different study population, the German DRS yielded a higher AUC value for detection of undiagnosed diabetes. For example, Rathmann *et al.* found an AUC value of 0.67 for the Cambridge DRS, 0.65 for the FINDRISK, and 0.61 for the Rotterdam Diabetes Study Questionnaire (33). Besides, in a study of Bergmann *et al.* the application of the German FINDRISK version yielded 0.75. Only Li *et al.* detected a higher accuracy (AUC=0.81) when applying the German FINDRISK version, and Rathmann *et al.* found an AUC value of 0.90 when applying the predictive clinical model of the San Antonio Heart Study (33, 36). However, both Li *et al.* and Bergmann *et al.* included history of high blood glucose in their score. It encompasses intermediate hyperglycaemia and diabetes itself, which is obviously positively related to identification of undiagnosed diabetes and therefore might yield to a higher accuracy for detection of undiagnosed diabetes. Furthermore, the predictive clinical model of the San Antonio Heart Study included invasive measures, which have been shown to improve accuracy (36). As a result, it is difficult to compare the AUC value of a score using only non-invasive measures, like the German DRS, and a score using further invasive measures.

With regard to identification of intermediate hyperglycaemia, in their study, Schulze *et al.* found a sensitivity/specificity of 74/71% (cut off ≥500) based on FPG between 100 and 125 mg/dl (40). In the present analyses, rather lower levels of sensitivity/specificity for the detection of intermediate hyperglycaemia were found (70.9/62.9% based on FPG; 67.7/67.2% based on HbA1c). Besides, while in the current investigation the German DRS yielded an AUC value of 0.72 (FPG) and 0.74 (HbA1c) for detection of intermediate hyperglycaemia, Schulze *et al.* found an AUC of 0.79 based on FPG in their study. This indicates a poorer

performance of the German DRS in the present investigation (40). However, the difference is rather moderate and it has been shown in previous studies that the performance of risk scores is better in the original study population than in other study populations (33, 42).

Differences in accuracy, but also in sensitivity and specificity, between different scores might further occur due to differences in diagnostic measures used for identification of cases of undiagnosed diabetes. For example, Li *et al.* and Rathmann *et al.* used both FPG ≥ 126 mg/dl and a 2 hour post-load glucose level of ≥ 200 mg/dl as diagnostic criteria (33, 36). In the present investigation FPG ≥ 126 mg/dl and HbA1c ≥ 6.5% were used. So far, HbA1c has not been used as diagnostic criterion in any of the studies assessed. Thus, further comparison of the current findings based on HbA1c with the performance of other scores was not possible.

4.2 Strengths and limitations

The current investigation is the first study applying a diabetes risk score to such a large representative sample of the residential population of Germany, comprising subjects aged 18-79 years. A weighting factor was used for all analyses to improve representativity. In addition, the applied German DRS was the only risk score developed based on a large German cohort study (EPIC-Potsdam), which improves its applicability in a German study population (48). Moreover, information about a high number of biomarkers related to pathophysiology of type 2 diabetes was available and could be included in the current analyses.

The present analyses is the only investigation examining the performance of a diabetes risk score in a German population by using HbA1c as diagnostic criterion for diabetes. HbA1c has been approved by WHO only recently in 2011 as new diagnostic criterion for diabetes (62). Therefore, it was used as diagnostic criterion only in a few studies yet and not in any of the studies assessed.

Finally, the score variables age, hypertension, height, waist circumference, former smoking, current smoking, and alcohol consumption were assessed in a similar way in EPIC-Potsdam and in the GNHIES, improving the comparability of results between the original study and the present evaluation.

Alongside with the presented strengths, there were also some limitations, which will be discussed in the following. Some population groups might still be underrepresented in the survey sample, e.g. it has been shown that poor self-rated health is more common among non-

participants of health surveys than among participants (73, 74). However, analysis of the self-reported health status of non-respondents of the GNHIES showed no major differences in self-rated health between respondents and non-respondents (52). Moreover, both GNHIES and EPIC-Potsdam only included certain age-groups. In the GNHIES people above the age of 80 years did not take part, therefore there might be differences between the performance of the German DRS among elderly and the performance of the score in the present investigation. On the other hand, in EPIC-Potsdam only women aged 35-65 years and men aged 40-65 years participated. As a result, the generalizability of the German DRS to age-groups younger than 35 years and older than 65 years might be limited. In addition, in both GNHIES and EPIC-Potsdam participants with migration background were underrepresented (52). Thus, the German DRS might show a different sensitivity, specificity and discriminatory ability among the general German population than among the current sample and among the EPIC-Potsdam sample.

One of the most commonly used measures for diagnosing diabetes, besides 2 hour post-load glucose level, is FPG. However, only serum glucose was analysed in the GNHIES and therefore had to be converted into plasma glucose before further analyses by using the equation of Carstensen *et al.* (63). In addition, there was only a lower number of fasting blood samples available. Therefore, only information of 1060 participants regarding fasting glucose levels could be used for analyses. However, as fasting is no prerequisite for measuring HbA1c (62), this information could be analysed for a higher number of participants (N=6032).

There were some differences in the assessment of the score variables between GNHIES and EPIC-Potsdam. Consumption of red meat, for example, was overestimated in the GNHIES, as participants were solely asked for overall meat intake and not differentiated for red meat and poultry consumption. However, compared to, e.g. age, waist circumference, and height the influence of red meat consumption to the overall score value is rather low. For example, on average men are 44.14 years old, 176.41 cm tall, and their waist circumference is 96.07 cm, while the average intake of red meat is only 0.63 portions per day. Moreover, for the core survey there was only information available about the frequencies of consumption of whole grain bread, red meat, and coffee, but not about the consumed amount per day. Thus, the average daily amount of intake could only be estimated for each category of the core survey's FFQ, based on data of a survey module consisting of a subsample of 4030 subjects. As a consequence, the nutritional components of the score were calculated based on the median

intake of each category of the core survey's FFQ, instead of taking the individual daily intake into account. Therefore, the intake of red meat, whole grain bread and coffee might have been over- or underestimated. However, due to the small daily intake of slices of whole grain bread, portions of red meat, and cups of coffee (for men on average 0.62 slices of whole grain bread, 0.63 portions of red meat, and 2.16 cups of coffee) the influence is rather small.

In addition, there were differences in the assessment of physical activity. While in EPIC-Potsdam sports, biking and gardening were assessed, in the GNHIES there was only a general question about sports participation. Furthermore, the questionnaire asked in categories. Therefore, for each category the time was estimated as middle time of each category band, i.e. less than 1 hour was allocated with a time of 0.5 hours, between 1 and 2 hours a time of 1.5 hours was assigned. People spending more than 4 hours per week on doing exercise were allocated with an average time of 4.5 hours per week. As a result, the average time per week spend on doing exercise might have been slightly overestimated for some groups and might have been underestimated for the highest category. However, the average time spent on physical activity is only 1.22 h/week among men and 0.95 h/week among women, and should therefore only have a small influence on the final level of the German DRS.

Finally, it has to be taken into account that in both GNHIES and EPIC-Potsdam most information relevant for calculation of the score was gathered through self-administered questionnaires and could therefore be susceptible to self-reporting bias. For example, there might have been misreporting for smoking, eating habits, and physical activity due to social desirability bias (10).

Contrarily, to the present study Rathmann *et al.* found a higher discriminatory ability of their prediction model among men than among women. However, their model was based on a study population aged 55-74 years where the influence of age was less important (31). Application of the German DRS in a subsample, including the same age-groups as in EPIC-Potsdam, showed further differences in the performance of the score among the whole survey population and among the subsample. These findings indicate that the performance of different scores might vary between men and women and between different age-groups.

5. Conclusion

All together, the present evaluation identified the German DRS as an accurate screening tool for undiagnosed diabetes and intermediate hyperglycaemia among the survey population. This

indicates that it could possibly be used as a screening tool for undiagnosed diabetes as well as for intermediate hyperglycaemia on population level. However, when implementing the German DRS as a screening tool, it should be considered that it showed a higher discriminatory ability among women than among men (higher AUC values).

Based on the current results, further research with regard to differences in discriminatory ability between women and men and between different age-groups would be useful. In addition, it would be worth to evaluate the ability of the German DRS to predict the risk of developing future diabetes by using longitudinal data. Besides, a comparison of the performance of different versions of the German DRS, e.g. classic version, and simplified version, would help to further assess the strengths of the German DRS. Finally, it would be useful to examine additional possibilities for identification of high risk groups for developing future diabetes improving efficiency of the German DRS as a screening tool among the German population.

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Appendix 1 – Stratification by gender

A) Undiagnosed diabetes

I) Sensitivity and specificity of the German DRS among women to identify undiagnosed diabetes at different cut points based on FPG ≥ 126 mg/dl (N = 660).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	23	100.0	541	84.9	15.1
≥ 400	23	100.0	416	65.3	34.7
≥ 500	22	95.7	260	40.8	59.2
≥ 600	15	65.2	135	21.2	78.8
≥ 700	11	47.8	44	6.9	93.1
≥ 800	6	26.1	4	0.6	99.4

FPR = false-positive rate (100-specificity)

II) Sensitivity and specificity of the German DRS among men to identify undiagnosed diabetes at different cut points based on FPG ≥ 126 mg/dl (N = 400).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	26	100.0	348	93.0	7.0
≥ 400	26	100.0	296	79.1	20.9
≥ 500	24	92.3	241	64.4	35.6
≥ 600	16	61.5	167	44.7	55.3
≥ 700	8	30.8	72	19.3	80.7
≥ 800	2	7.7	17	4.5	95.5

FPR = false-positive rate (100-specificity)

III) Sensitivity and specificity of the German DRS among women to identify undiagnosed diabetes at different cut points based on HbA1c ≥ 6.5 % (N = 3076).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	99	100.0	2400	80.6	19.4
≥ 400	97	98.0	1698	57.0	43.0
≥ 500	90	90.9	1046	35.1	64.9
≥ 600	67	67.7	507	17.0	83.0
≥ 700	35	35.4	168	5.6	94.4
≥ 800	8	8.1	28	0.9	99.1

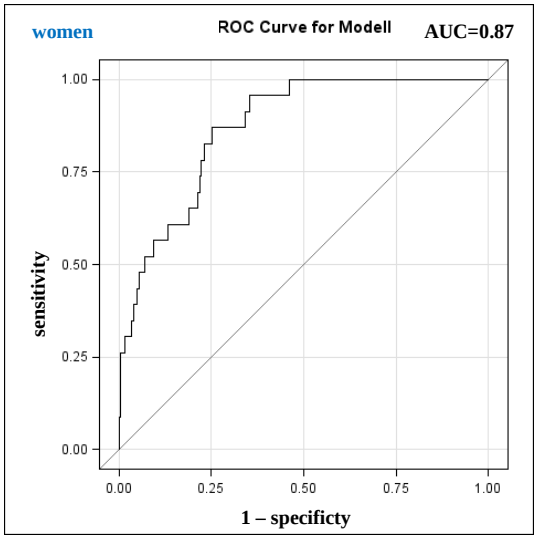
FPR = false-positive rate (100-specificity)

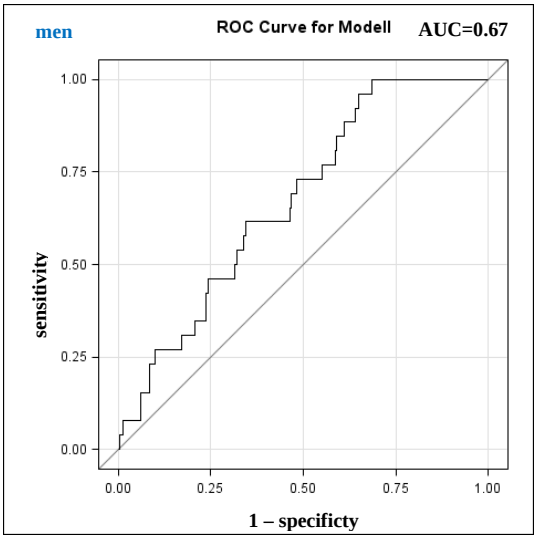
IV) Sensitivity and specificity of the German DRS among men to identify undiagnosed diabetes at different cut points based on HbA1c ≥ 6.5 % (N = 2956).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	139	99.3	2592	92.0	8.0
≥ 400	138	98.6	2122	75.4	24.6
≥ 500	128	91.4	1469	52.2	47.8
≥ 600	105	75.0	749	26.6	73.4
≥ 700	58	41.4	238	8.5	91.5
≥ 800	15	10.7	35	1.2	98.8

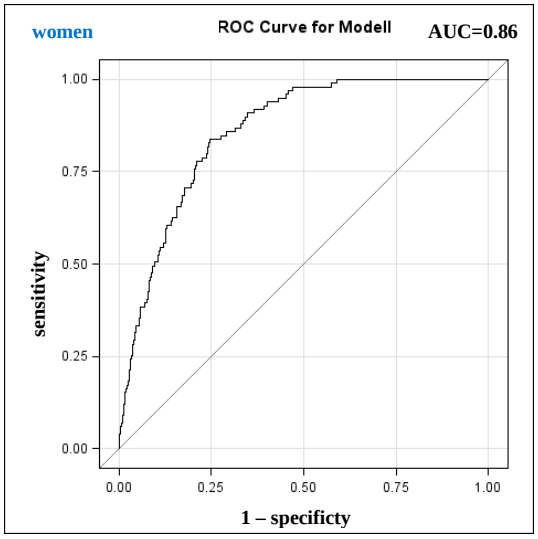
FPR = false-positive rate (100-specificity)

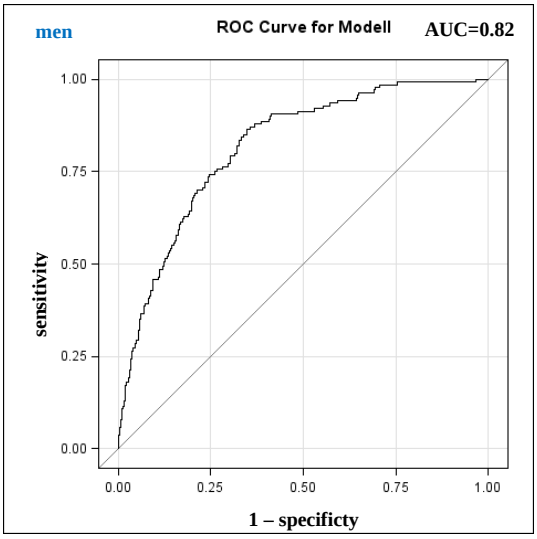
I) ROC curve of the German DRS for prediction of undiagnosed diabetes among women (N=660) and men (N=400) using FPG ≥126 mg/dl.





II) ROC curve of the German DRS for prediction of undiagnosed diabetes among women (N=3076) and men (N=2956) using HbA1c ≥6.5%.





B) Intermediate hyperglycemia

V) Sensitivity and specificity of the German DRS among women to identify intermediate hyperglycaemia at different cut points based on FPG 100 – 125 mg/dl (N = 637).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	183	95.8	358	80.3	19.7
≥ 400	167	87.4	249	55.8	44.2
≥ 500	130	68.1	130	29.1	70.9
≥ 600	76	39.8	59	13.2	86.8
≥ 700	24	12.6	20	4.5	95.5
≥ 800	1	0.5	3	0.7	99.3

FPR = false-positive rate (100-specificity)

VI) Sensitivity and specificity of the German DRS among men to identify intermediate hyperglycaemia at different cut points based on FPG 100 – 125 mg/dl (N = 373).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	177	96.7	171	89.5	10.5
≥ 400	163	89.1	133	69.6	30.4
≥ 500	135	73.8	106	55.5	44.5
≥ 600	103	56.3	64	33.5	66.5
≥ 700	49	26.8	23	12.0	88.0
≥ 800	14	7.7	3	1.6	98.4

FPR = false-positive rate (100-specificity)

VII) Sensitivity and specificity of the German DRS among women to identify intermediate hyperglycaemia at different cut points based on HbA1c 5.7 – 6.4 % (N = 2977).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	781	95.5	1619	75.0	25.0
≥ 400	700	85.6	998	46.2	53.8
≥ 500	539	65.9	507	23.5	76.5
≥ 600	325	39.7	182	8.4	91.6
≥ 700	123	15.0	45	2.1	97.9
≥ 800	23	2.8	5	0.2	99.8

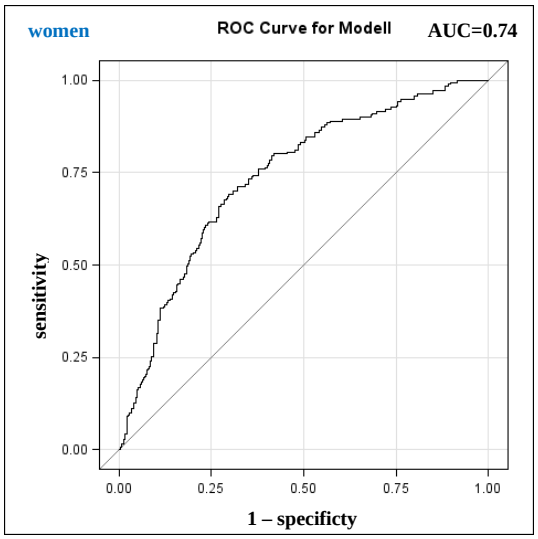
FPR = false-positive rate (100-specificity)

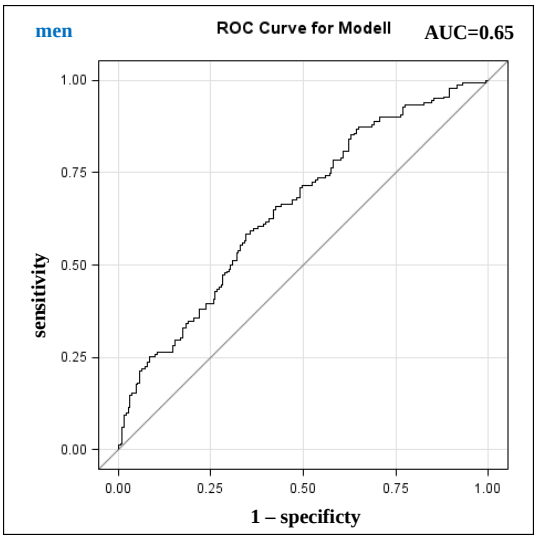
VIII) Sensitivity and specificity of the German DRS among men to identify intermediate hyperglycaemia at different cut points based on HbA1c 5.7 – 6.4 % (N = 2816).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	905	96.1	1687	90.0	10.0
≥ 400	820	87.05	1302	69.5	30.5
≥ 500	653	69.3	816	43.5	56.5
≥ 600	368	39.1	381	20.3	79.7
≥ 700	133	14.1	105	5.6	94.4
≥ 800	24	2.5	11	0.6	99.4

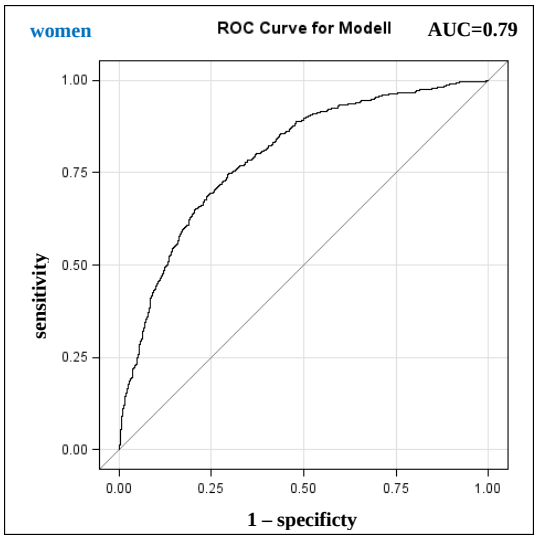
FPR = false-positive rate (100-specificity)

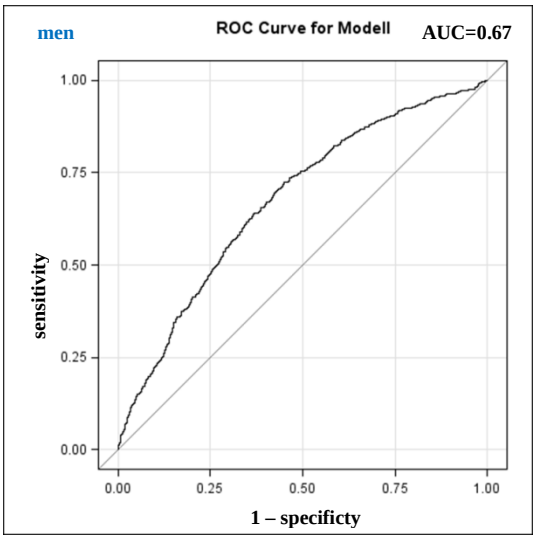
III) ROC curve of the German DRS for prediction of intermediate hyperglycaemia among women (N=637) and men (N=373) using FPG 100-125 mg/dl.





IV) ROC curve of the German DRS for prediction of intermediate hyperglycaemia among women (N=2977) and men (N=2816) using HbA1c 5.7-6.4%.





Appendix 2 – Analyses for a subpopulation: women aged 35-65 years, men aged 40-65 years

Descriptive statistics

Characteristics among men (N = 1457) and women (N = 1931) of the study population.

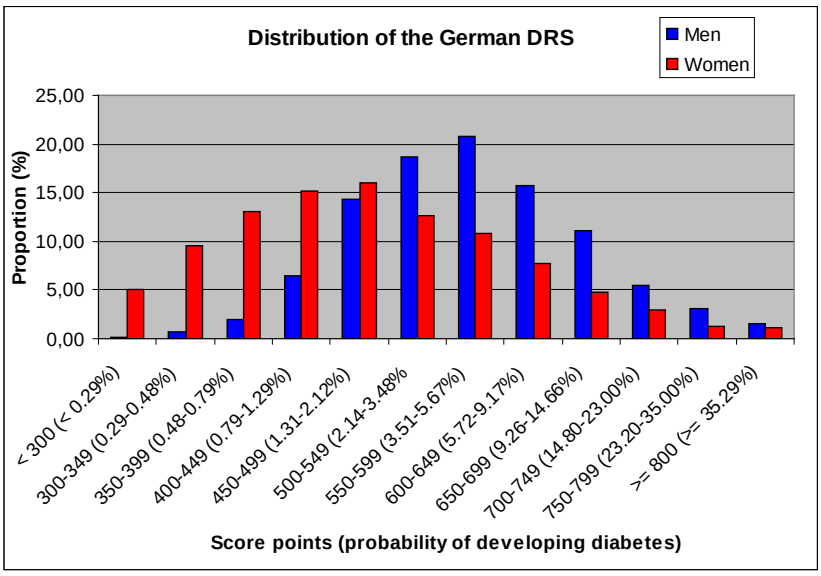
	Men N = 1457	Women N = 1931	P value
Components of the German DRS			
Age (years)	51.51 (51.09 – 51.92)	49.17 (48.73 – 49.61)	< 0.0001
Waist circumference (cm)	99.62 (99.08 – 100.17)	85.86 (85.27 – 86.44)	< 0.0001
Height (cm)	175.35 (174.99 – 175.71)	163.30 (163.01 – 163.60)	< 0.0001
Physical activity (h/week)	1.05 (0.97 – 1.12)	0.94 (0.88 – 1.01)	0.3224
Moderate alcohol consumption (10-40 g/day) (%)	36.5%	13.6%	< 0.0001
Hypertension (%)	25.09%	23.12%	0.1961
Meat consumption (portions [each 150g]/day)	0.62 (0.61 – 0.63)	0.57 (0.57 – 0.58)	< 0.0001
Whole grain bread consumption (slices [each 50g]/day)	0.66 (0.63 – 0.70)	0.84 (0.81 – 0.87)	< 0.0001
Coffee consumption (cups [each 150g]/day)	2.32 (2.25 – 2.39)	2.35 (2.29 – 2.41)	0.2252
Former smoker (%)	34.29%	19.52%	< 0.0001
Current heavy smoking (%) ≥20 cigarettes/day	15.61%	9.47%	< 0.0001
DRS points	573.38 (567.99 – 578.77)	482.73 (476.88 – 488.58)	< 0.0001
Probability of developing diabetes (%)	6.86% (6.41 – 7.32)	3.9% (3.59 – 4.22)	< 0.0001
Biomarker of type 2 diabetes			
Plasmaglucose (mg/dl)	101.00 (100.12 – 101.89)	96.28 (95.68 – 96.89)	< 0.0001
HbA1c (%)	5.58 (5.54 – 5.62)	5.43 (5.40 – 5.45)	< 0.0001
HDL-cholesterol (mg/dl)	48.45 (47.63 – 49.28)	63.79 (62.93 – 64.66)	< 0.0001
Triglyceride (mg/dl)	164.77 (159.35 – 170.36)	105.57 (102.97 – 108.23)	< 0.0001
Cholesterol (mg/dl)	242.64 (240.14 – 245.16)	234.61 (232.44 – 236.80)	< 0.0001
γ-glutamyltransferase (GGT) (U/l)	20.34 (19.63 – 21.07)	12.20 (11.85 – 12.55)	< 0.0001
Alanin aminotransferase (ALT) (U/l)	16.12 (15.72 – 16.52)	10.30 (10.09 – 10.51)	< 0.0001

Values are given as weighted arithmetic mean (95% confidence interval) or weighted percentage for all Diabetes-Risk Score components and as weighted geometric means (95% confidence interval) for all logarithmically transformed biomarkers.

Mean fasting plasma glucose was 104.85 mg/dl (CI: 102.00 mg/dl – 107.78 mg/dl) for men (N=177)and 96.78 mg/dl (CI: 95.38 mg/dl – 98.19 mg/dl) for women (N=444) (p-value: < 0.0001). Mean fasting triglycerides was 136.55 mg/dl (CI: 125.13 mg/dl – 149.00 mg/dl) for men and 96.78 mg/dl (95.38 mg/dl – 98.19 mg/dl) for women (N=444) (p-value: < 0.0001).

Distribution

Distribution of the German DRS and the probability of developing diabetes among men (N = 1457) and women (N = 1931) in a national sample of the German population.



Correlation

Pearson correlation among men (N = 1457) and women (N = 1931) between German DRS and biomarkers of type 2 diabetes.

Biomarker	Men N = 3142	Women N = 3264
Glucose (mg/dl)	0.21	0.30
HbA1c (%)	0.20	0.45
HDL-cholesterol (mg/dl)	-0.22	-0.29
Triglyceride (mg/dl)	0.24	0.47
Cholesterol (mg/dl)	0.12	0.32
γ-glutamyltransferase (GGT) (U/l)	0.23	0.34
Alanintransferase (ALT) (U/l)	0.22	0.41

All biomarkers were logarithmically transformed. All correlation coefficients were significant at a level of $p < 0.0001$.

Among a subsample of men (N = 181) and women (N = 449) who fasted overnight glucose was significantly correlated with the computed German DRS (correlation coefficient: men: 0.21 (p=0.0061); women: 0.33 (p<0.0001)). Besides, there was a significant ($p < 0.0001$) correlation between triglycerides and the German DRS among both genders (correlation coefficient: men: 0.29; women: 0.44).

Performance

Sensitivity and specificity of the German DRS to identify undiagnosed diabetes at different cut points based on FPG ≥ 126 mg/dl (N = 621).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	30	100.0	571	96.6	3.4
≥ 400	30	100.0	490	82.9	17.1
≥ 500	27	90.0	326	55.2	44.8
≥ 600	16	53.3	174	29.4	70.6
≥ 700	6	20.0	58	9.8	90.2
≥ 800	2	6.7	10	1.7	98.3

FPR = false-positive rate (100-specificity)

Sensitivity and specificity of the German DRS to identify undiagnosed diabetes at different cut points based on HbA1c ≥ 6.5 % (N = 3223).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	136	100.0	2994	97.0	3.0
≥ 400	133	97.8	2559	82.9	17.1
≥ 500	119	87.5	1732	56.1	43.9
≥ 600	87	64.0	780	25.3	74.7
≥ 700	41	30.1	207	6.7	93.3
≥ 800	9	6.6	31	1.0	99.0

FPR = false-positive rate (100-specificity)

Sensitivity and specificity of the German DRS to identify intermediate hyperglycaemia at different cut points based on FPG 100 – 125 mg/dl (N = 591).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	225	98.3	346	95.6	4.4
≥ 400	214	93.4	276	76.2	23.8
≥ 500	163	71.2	163	45.0	55.0
≥ 600	98	42.8	76	21.0	79.0
≥ 700	37	16.2	21	5.8	94.2
≥ 800	7	3.1	3	0.8	99.2

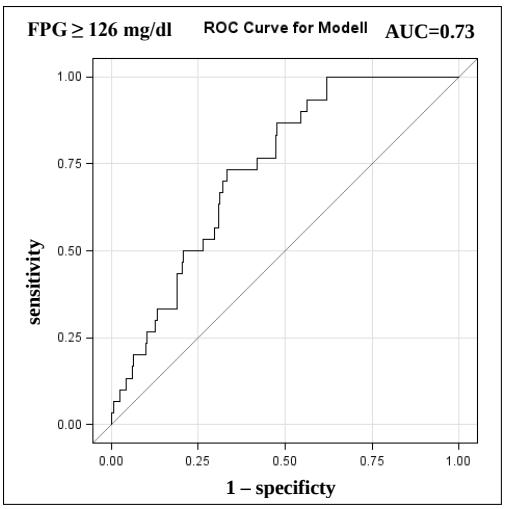
FPR = false-positive rate (100-specificity)

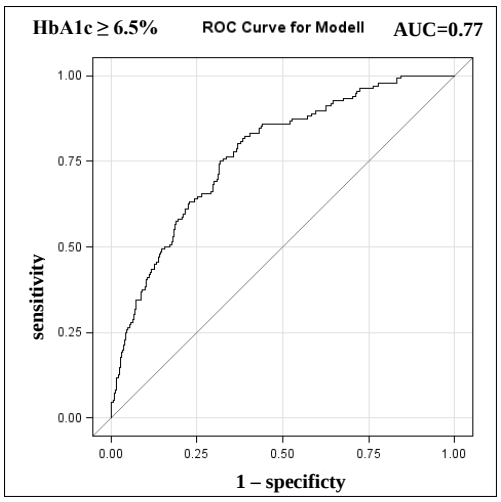
Sensitivity and specificity of the German DRS to identify intermediate hyperglycaemia at different cut points based on HbA1c 5.7 – 6.4 % (N = 3087).

Score	Number of prevalent cases	Sensitivity (%)	Number of non-prevalent cases	FPR (%)	Specificity (%)
≥ 300	1059	99.1	1935	95.9	4.1
≥ 400	998	93.4	1561	77.4	22.6
≥ 500	781	73.1	951	47.1	52.9
≥ 600	405	37.9	375	18.6	81.4
≥ 700	117	10.9	90	4.5	95.5
≥ 800	24	2.2	7	0.3	99.7

FPR = false-positive rate (100-specificity)

ROC curve of the German DRS for prediction of undiagnosed diabetes using FPG ≥126 mg/dl (N = 621) and using HbA1c ≥6.5% (N = 3223).





ROC curve of the German DRS for prediction of intermediate hyperglycaemia using FPG 100-125 mg/dl (N = 590) and using HbA1c 5.7-6.4% (N = 3087).