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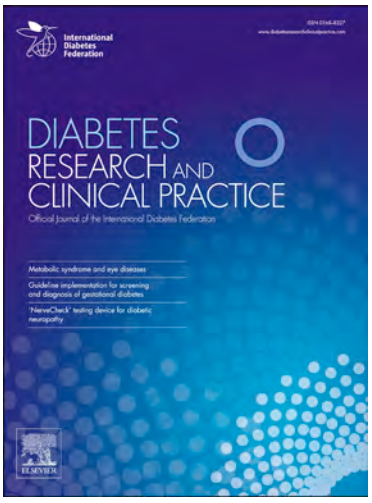

Evaluation of the Finnish Diabetes Risk Score as a screening tool for undiagnosed type 2 diabetes and dysglycaemia among early middle-aged adults in a large-scale European cohort. The Feel4Diabetes-study

Christina Mavrogianni, Christina-Paulina Lambrinou, Odysseas Androutsos, Jaana Lindström, Jemina Kivelä, Greet Cardon, Nele Huys, Kaloyan Tsochev, Violeta Iotova, Nevena Chakarova, Imre Rurik, Luis A. Moreno, Stavros Liatis, Konstantinos Makrilakis, Yannis Manios, on behalf of the Feel4Diabetes-study group,

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Title page

Title: Evaluation of the Finnish Diabetes Risk Score as a screening tool for undiagnosed type 2 diabetes and dysglycaemia among early middle-aged adults in a large-scale European cohort. The Feel4Diabetes-study

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Structured Abstract

Aim: To assess the diagnostic accuracy of the FINDRISC for undiagnosed type 2 diabetes mellitus (T2DM) and dysglycaemia (i.e. the presence of prediabetes or T2DM) among early middle-aged adults from vulnerable groups in a large-scale European cohort.

Methods: Participants were recruited from low-socioeconomic areas in high-income countries (HICs) (Belgium-Finland) and in HICs under austerity measures (Greece-Spain) and from the overall population in low/middle-income countries (LMICs) (Bulgaria-Hungary). Study population comprised of 2,116 parents of primary-school children from families identified at increased risk of T2DM, based on parental self-reported FINDRISC. Sensitivity (Se), specificity (Sp), area under the receiver operating characteristic curves (AUC-ROCs) and the optimal cut-offs of FINDRISC that indicate an increased probability for undiagnosed T2DM or dysglycaemia were calculated.

Results: The AUC-ROC for undiagnosed T2DM was 0.824 with optimal cut-off≥14 (Se=68%, Sp=81.7%) for the total sample, 0.839 with optimal cut-off≥15 (Se=83.3%, Sp=86.9%) for HICs, 0.794 with optimal cut-off≥12 (Se=83.3%, Sp=61.1%) for HICs under austerity measures and 0.882 with optimal cut-off≥14 (Se=71.4%, Sp=87.8%) for LMICs. The AUC-ROC for dysglycaemia was 0.663 with optimal cut-off≥12 (Se=58.3%, Sp=65.7%) for the total sample, 0.656 with optimal cut-off≥12 (Se=54.5%, Sp=64.8%) for HICs, 0.631 with optimal cut-off≥12 (Se=59.7%, Sp=62.0%) for HICs under austerity measures and 0.735 with optimal cut-off≥11 (Se=72.7%, Sp=70.2%) for LMICs.

Conclusion: FINDRISC can be applied for screening primarily undiagnosed T2DM but also dysglycaemia among vulnerable groups across Europe, considering the use of different cut-offs for each subpopulation.

Keywords: Type 2 diabetes mellitus; FINDRISC; Diabetes screening; Diabetes prevention; Vulnerable groups

Abbreviation list:

BMI: Body Mass Index
FINDRISC: Finnish Diabetes Risk Score
FPG: Fasting plasma glucose
T2DM: Type 2 Diabetes Mellitus
HICs: High-income countries
IFG: Impaired fasting glucose
IGT: Impaired glucose tolerance
LMICs: Low/middle-income countries
OGTT: Oral glucose tolerance test
ROC: Receiver Operating Characteristic

1. Introduction

Diabetes mellitus is one of the largest global health emergencies of the 21st century, with increasing prevalence worldwide, that currently affects 8.8% of the adult population [1]. Type 2 diabetes mellitus (T2DM) accounts for about 90% of all diabetes cases, while a major public-health challenge is that about 50% of these cases remain undiagnosed [1]. Since T2DM does not cause specific symptoms for many years, detection is often delayed and advanced complications are frequently present at the time of diagnosis [2, 3]. In addition, prediabetes -i.e. an intermediate hyperglycemic state characterized by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)- is a risk factor for developing T2DM with the annual incidence of T2DM in individuals with different prediabetes stages (IFG, IGT, and both) to vary from 5 to 10%[4]. As there is evidence that early detection of T2DM may reduce mortality and the risk of complications [5, 6], and that the identification of people with prediabetes followed by lifestyle and/or pharmacological interventions can prevent or delay T2DM [7, 8], the implementation of screening strategies for its early diagnosis and prevention is reasonable [9].

There is a variation in the burden of diabetes among population groups. About 79% of adults with diabetes live in low/middle-income countries (LMICs) [1], while low educational level and high unemployment rate in high income countries (HICs) have been associated with increased risk of T2DM [10]. Moreover, 84.5% of all people with undiagnosed diabetes live in LMICs, while even in HICs 37.3% of people with diabetes have undiagnosed disease [1]. These inequalities may also further vary among HICs, since the global financial crisis has an adverse impact on population health and access to care; especially in countries that suffered the strictest austerity measures [11]. Thus, a large segment of the population in LMICs, as well as low socioeconomic groups in HICs could be considered as vulnerable for developing T2DM. Given the increasing T2DM prevalence [1], identifying T2DM at early stage becomes a public health priority, especially in vulnerable population groups.

According to the current guidelines, T2DM diagnosis can be based on measurements of either fasting plasma glucose (FPG), 2h glucose value after an oral glucose tolerance test (OGTT) or glycated haemoglobin (HbA1c) [12, 13]. However, these methods are invasive, time-consuming and expensive [14], hence not suitable for mass screening. Furthermore, since they provide information only by measuring glycaemia, it would be more efficient to also identify individuals at high risk of T2DM when being in normoglycaemic state, in order to prevent prediabetes and overt T2DM by implementing effective interventions. Thus, a number of risk scores have been developed worldwide from different settings and populations, both for detection of undiagnosed T2DM and for identification of individuals at future risk [15-17]. In this context, international health organizations [12, 13, 18] recommend the use of validated diabetes risk scores to guide health care professionals on whether performing a diagnostic test is appropriate.

The Finnish Diabetes Risk Score (FINDRISC) was developed for the Finnish National T2DM Prevention Programme [19] to facilitate identification of people at increased risk and it is the most commonly used diabetes risk score in Europe. Previous studies have evaluated the FINDRISC in detecting undiagnosed T2DM and/or prediabetes in many European [20-26] and

other countries [27-31], with good validity results in most of these populations. Simplified versions of the FINDRISC have been also tested and were found to be equally efficient as FINDRISC [22, 25, 28]. However, previous validation studies of the FINDRISC conducted in Europe are based on data collected from one country and have not taken into consideration socioeconomic criteria or focused on vulnerable groups. Furthermore, the study population in these studies included middle-aged or old participants [20-26] or patients with one or more cardiovascular risk factors [21, 22, 26], usually recruited using opportunistic screening methods (i.e. among those individuals attending general practitioners' offices or health care centres) [21, 23, 26] or as a random population sample [20, 22, 24, 25]. Thus community-based evaluations of the FINDRISC among vulnerable groups in multi-centre studies seem to be essential in order to examine its general applicability and accuracy to screen for glucose metabolism disorders, as well as to provide a rational basis to refer high risk individuals for glycaemia testing so that to confirm diagnosis.

The primary aims of current study were to (i) assess the diagnostic accuracy of the FINDRISC in detecting undiagnosed T2DM and dysglycaemia among early middle-aged adults in a large-scale European cohort and (ii) examine any potential differences in FINDRISC performance among LMICs and vulnerable groups in HICs and HICs under austerity measures. A secondary aim was to examine which FINDRISC components were most strongly associated with these outcomes, so that to further support the development and use of simplified versions.

2. Material and methods

2.1. Study background

The current study used the baseline data of the EU-funded Feel4diabetes-study (http://feel4diabetes-study.eu/), which aimed to develop, implement and evaluate a school- and community-based intervention to prevent T2DM among families from vulnerable groups across Europe. The Feel4Diabetes-study was registered at clinicaltrials.gov as NCT02393872.

2.2. Study protocol and recruitment

A detailed description of methods has been previously published [32]. In brief, recruitment was based on a standardized, multi-stage sampling procedure and was conducted within selected provinces in six European countries, targeting population-groups that were vulnerable for developing T2DM. In Bulgaria and Hungary (i.e. LMICs), all families were considered vulnerable and eligible to participate in the study, while in Belgium, Finland, Greece and Spain (i.e. HICs), families from municipalities with the lowest educational level or the highest unemployment rate (as retrieved from official resources and authorities) were included as vulnerable groups. In each country, primary schools located in the selected municipalities were used as the entry-point to the community and the children attending the first three grades of compulsory education, as well as their parents and/or grandparents, were recruited to the study.

Self-administrated FINDRISC questionnaires were collected from 20,547 parents (53.7% females) from 11,395 families. Of these families, those at higher risk of developing T2DM (further mentioned as "high-risk families") were identified. A family was identified as "high risk" if at least one parent had FINDRISC ≥10, considering the young age of the participants. Following this first screening via school setting, all the parents and/or grandparents of the "high-risk families", irrespectively of their individually calculated FINDRISC, were invited to undergo a more detailed assessment (second screening) delivered in local community centers or during home visits (in Belgium).

From the identified "high-risk families", 3,148 parents from 2,535 families underwent the second screening. Of these, 83 (2.64%) participants were excluded from the current analysis because of previously diagnosed diabetes, 429 (13.6%) participants due to missing FPG data, 117 (3.72%) participants due to incomplete information to calculate FINDRISC and 403 (12.8%) participants due to missing other questionnaire or measurement data.

In all countries, measurements were conducted by thoroughly trained research assistants, using standardized protocols and calibrated equipment. Recruitment started on January 2016 and measurements were conducted between April-June and for Finland, Hungary and Bulgaria were extended during August-September 2016.

2.3. Measures

Questionnaire data: During the first screening, all parents were requested to complete the most recent version of the FINDRISC questionnaire, which consists of eight scored questions that cover the well-known risk factors of T2DM, i.e. age, body mass index (BMI), waist circumference (WC), daily physical activity, daily consumption of vegetables and fruits/ berries, use of antihypertensive medication, history of high blood glucose, and family history of diabetes [33]. The total score indicates the individual's 10-year risk of developing T2DM and ranges from 0 to 26, as follows: <7 (low), 7-11 (slightly elevated), 12-14 (moderate), 15-20 (high) and >20 (very high). In order to facilitate the assessment of WC, a paper measuring waist tape was provided to all participants. Standardized questionnaires were also used to collect data related to participants' sociodemographics.

Anthropometry: Body weight and height were measured in light clothing and without shoes to the nearest 0.1kg and 0.1cm respectively, and WC was measured midway between the lowest rib margin and the iliac crest to the nearest 0.1cm. Portable equipment was used (for weight: digital scales, for height: telescopic stadiometers, for WC: non-elastic tapes). BMI and WC were classified based on the World Health Organization (WHO) criteria [34].

Blood pressure measurement: Blood pressure was measured on the right arm, in a sitting position using electronic sphygmomanometers (OMRON M6 or OMRON M6 AC) after five minutes of rest, on three occasions, at one minute interval.

Blood indices: Blood samples were drawn in the morning after overnight fasting (duration: eight hours or longer). FPG and serum total and high-density lipoprotein (HDL) cholesterol and triglyceride levels were analyzed in accredited laboratories, using similar enzymatic assays in all study centers. Low-density lipoprotein (LDL) cholesterol was calculated using the

Friedewald formula [35]. Participants without previously diagnosed diabetes were classified according to the WHO criteria [36], as: normal (FPG<6.1mmol/L), prediabetes (FPG 6.1-6.9mmol/L) and T2DM (FPG≥7.0mmol/L). Dysglycaemia was defined as the presence of prediabetes or T2DM.

2.4. Ethics statement

The Feel4Diabetes-study adhered to the Declaration of Helsinki and the conventions of the Council of Europe on human rights and biomedicine. All participating countries obtained ethical clearance from the relevant ethical committees and local authorities. All participants gave their written informed consent prior to their enrolment in the study.

2.5. Statistical analysis

In the current analysis the participating countries were grouped to country categories as: HICs (Belgium-Finland), HICs under austerity measures (Greece-Spain) and LMICs (Bulgaria-Hungary). Descriptive data on participants' characteristics are presented as means± standard deviations or percentages for continuous or categorical values, respectively. For between-group comparisons, One-Way Analysis of Variance or Kruskall-Wallis was used for continuous variables, while the Pearson's Chi-square test was used to compare percentages.

Receiver operating characteristic (ROC) analysis was used to assess the accuracy of the FINDRISC in detecting undiagnosed T2DM and dysglycaemia. The area under the ROC curves (AUC-ROCs) were plotted, while sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were calculated for FINDRISC values from 11 to 16. The optimal cut-offs were determined by the point with the shortest distance to (0,1) in the ROC curve that maximizes the Se and Sp of the test. The distance for each observed cut-off was calculated as the square root of $[(1\text{-Se})^2 + (1\text{-Sp})^2]$ [37].

Multivariate logistic regression models were constructed to estimate the association of FINDRISC value and its separate components with undiagnosed T2DM and dysglycaemia. These analyses were adjusted for potential confounders (sex, educational level and country category). All statistical tests were two-tailed and the level of statistical significance was set at $P<0.05$. The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 21.0 and the MedCalc (MedCalc Software bvba, Ostend, Belgium), version 18.6.

3. Results

Table 1 presents the descriptive characteristics of the 2,116 participants, stratified by country category. Participants were aged 41.1±5.48 years and 67.3% were women. The overall prevalence of unemployment was 5.1%, higher in HICs under austerity measures compared with HICs and LMICs (8.4% vs. 2.5% and 0.7%, respectively, P<0.05). About one quarter of participants had less than 12 years of education (22.9%) and were current smokers (25.9%), with these percentages being statistically significant lower in HICs compared with other country categories. According to FPG and the WHO criteria, the overall prevalence of undiagnosed T2DM was 1.2%, without significant differences among country

categories, while for prediabetes it was 5.6%, higher in HICs compared with LMICs (8.0% vs. 3.5%, P<0.05). In the total sample, mean FINDRISC value was 10.2±4.06 (range 0-22), lower in LMICs compared with HICs and HICs under austerity measures (8.35±4.71 vs. 10.5±3.70 and 10.8±3.70, respectively, P<0.05). Statistically significant differences were observed among country categories in the percentages of FINDRISC components. A higher percentage of participants in HICs had positive history of high blood glucose or family history of diabetes, while a lower percentage of participants in HICs under austerity measures belonged to the younger age categories, was physically active for at least 30 minutes daily and consumed vegetables and fruits/berries every day. Regarding LMICs, a higher percentage of participants belonged to lower categories of BMI and WC and was under antihypertensive medication.

Table 2 presents the clinical characteristics of study participants across three FINDRISC categories (values: 0-11, 12-14, 15-26). As expected, age, prevalence of obesity and central obesity (defined as WC higher than 88cm or 102cm for women and men, respectively), but also blood pressure, FPG, cholesterol and triglyceride levels increased with greater FINDRISC (P<0.05 for all indices). A marked increase in the prevalence of undiagnosed T2DM and prediabetes was observed as FINDRISC values increased (P<0.001). Indicatively, in participants with FINDRISC≥15, the prevalence of undiagnosed T2DM and prediabetes was 5.1% and 10.7%, respectively.

The AUC-ROC for detecting undiagnosed T2DM (Figure 1A) was 0.824 (95% CI:0.755-0.893) for the total sample; 0.839 (95% CI:0.643-1.000) for HICs, 0.794 (95% CI:0.693-0.895) for HICs under austerity measures and 0.882 (95% CI:0.813-0.951) for LMICs. The AUC-ROC for detecting dysglycaemia (Figure 1B) was 0.663 (95% CI:0.615-0.710) for the total sample, 0.656 (95% CI:0.579-0.733) for HICs, 0.631 (95% CI:0.559-0.702) for HICs under austerity measures and 0.735 (95% CI:0.617-0.854) for LMICs. No statistically significant differences in the AUC-ROCs were found among country categories for both outcomes (P>0.05 for all pairwise comparisons). Table 3 shows the FINDRISC characteristics (Se, Sp, PPV, NPV), using different cut-offs for identifying undiagnosed T2DM or dysglycaemia. The optimal cut-off for undiagnosed T2DM was ≥14 for the total sample (Se=68.0%; Sp=81.7%) and for LMICs (Se=71.4%; Sp=87.8%), ≥15 for HICs (Se=83.3%; Sp=86.9%) and ≥12 for HICs under austerity measures (Se=83.3%; Sp=61.1%). Regarding dysglycaemia, the optimal cut-off was ≥12 for the total sample (Se=58.3%; Sp=65.7%), as well as for HICs (Se=54.5%; Sp=64.8%) and for HICs under austerity measures (Se=59.7%; Sp=62.0%), while ≥11 for LMICs (Se=72.7%; Sp=70.2%).

Results from logistic regressions showed significant associations of the FINDRISC with undiagnosed T2DM and dysglycaemia. One unit increase in the FINDRISC value was associated with a 35.6% (95% CI:22.0%-50.8%) increased odds of having undiagnosed T2DM and an 18.3% (95% CI:12.8%-24.1%) increased odds of having dysglycaemia, after adjusting for sex, educational level and country category (data not shown). Multivariate logistic regression analyses, as presented in Table 4, revealed the variables most strongly associated with undiagnosed T2DM to be BMI higher than 30kg/m^2 (OR=2.82; 95% CI:1.04-7.66), regular use of antihypertensive medication (OR=2.63; 95% CI:1.03-6.69) and history of high blood glucose (OR=6.23; 95% CI:2.57-15.1). Significant associations were also observed

between dysglycaemia and BMI higher than 30kg/m^2 (OR=1.80; 95% CI:1.18-2.74) and history of high blood glucose (OR=3.89; 95% CI: 2.60-5.83).

4. Discussion

The increasing prevalence of T2DM emphasizes the need to develop and implement better strategies for its early diagnosis and prevention. A simple first-level screening for prediabetes and T2DM through the use of non-laboratory and valid risk scores, followed by glycaemia testing for those individuals having a score considered high can be a cost-effective and practical method [12, 13, 18, 38]. As part of the Feel4Diabetes-study, we assessed the accuracy of the FINDRISC in detecting undiagnosed T2DM and dysglycaemia among vulnerable groups in Europe, highlighting the need to prioritize these populations to close the gap in health and social inequalities. Given the variability in the current population characteristics, AUC-ROCs and optimal cut-offs were also compared and provided separately for HICs (Belgium-Finland), HICs under austerity measures (Greece-Spain) and LMICs (Bulgaria-Hungary).

In the current study, including a population of pre-selected adults with increased T2DM risk and/or their spouses irrespectively of their individual risk, the FINDRISC was found to perform reasonably well in identifying undiagnosed T2DM (AUC-ROC for the total sample: 0.824; for HICs: 0.839; for HICs under austerity measures: 0.794; for LMICs: 0.882). These figures are in accordance with those obtained from other European countries so far, ranging from 0.62 to 0.81 [19-26]. Regarding dysglycaemia, the diagnostic accuracy of the FINDRISC was fair (AUC-ROC for the total sample: 0.663; for HICs: 0.656; for HICs under austerity measures: 0.631; for LMICs: 0.735), also comparable with the results of relevant studies, ranging from 0.52 to 0.72 [20, 21, 23-26]. As no statistically significant differences were observed among country categories in our study, it seems that the FINDRISC could be used as an equally accurate screening tool among the different vulnerable groups across Europe.

To be used as an initial screening tool, a risk score should have a sufficient proportion of individuals correctly identified as diseased (high Se) and rule out those without the disease with high probability (high NPV) [39]. In the total sample, using an optimal FINDRISC cut-off ≥14 and ≥12, the FINDRISC was able to identify 68% of those with undiagnosed T2DM and 58.3% of those with dysglycaemia, respectively. The corresponding NPVs for these cut-offs were 99.5% and 95.6%. The cut-offs for undiagnosed T2DM found in the current study are close to those reported by other studies from Southern [20, 23, 25], Central [22] and Eastern Europe [26], but higher than those suggested by the FINRISK surveys [19, 24] and the IGLOO study [21], while among the studies that also examined dysglycaemia, lower [21, 25, 26] and higher [20, 23] cut-offs have been provided. Furthermore, different optimal cut-offs were found for each country category for detecting undiagnosed T2DM and dysglycaemia, respectively: ≥15 and ≥12 for HICs; ≥12 for both conditions for HICs under austerity measures; and ≥14 and ≥11 for LMICs. The different optimal cut-offs observed for each one of the subpopulations could be due to differences among country categories in the prevalence of T2DM or dysglycaemia, as well as in several other population characteristics (e.g. lifestyle, socio-demographic factors). Correspondingly, Zhang et al. [31] identified

different optimal cut-offs by racial/ ethnic group among U.S. population. These findings support the application of different optimal cut-offs to different subgroups, highlighting also the rationality of evaluating the FINDRISC before applying it to a specific population.

As there are several methodological differences between the studies that have previously validated the FINDRISC, the current study should be compared to these with caution. Compared to previous studies conducted in Europe so far, our study sample comprised of younger adults (parents of primary-school children), apparently healthy that were recruited via the school-setting, using a systematic community-based approach. Furthermore, the gold standard used for the evaluation of the FINDRISC and the relevant diagnostic criteria may also play a role. In the majority of studies, the OGTT and/or FPG were considered the gold standard and the WHO criteria were used for T2DM and/or prediabetes diagnosis [19, 21-24, 26], while three recent studies used OGTT, FPG and HbA1c methods [20, 25, 31]. Two of these studies [20, 25] examined the use of OGTT, FPG and HbA1c separately in detecting undiagnosed T2DM and dysglycaemia in Spanish populations. Based on FPG and the American Diabetes Association criteria [37], in the study of Salinero-Fort et al. [25], the AUC-ROC for undiagnosed T2DM was 0.68 with optimal cut-off ≥13, while the AUC-ROC for dysglycaemia was 0.60 with optimal cut-off ≥11. Respectively, Costa et al. [20] proposed an optimal cut-off ≥14 for both conditions and concluded that OGTT and FPG have better overall discriminatory power than HbA1c. Last but not least, methodological differences regarding the FINDRISC data should be also taken into consideration, as in some studies shortened versions have been used [19, 21, 22], while in others the questionnaire was not self-administrated [20, 31].

It has been proposed that a simplified version of the FINDRISC could improve its efficiency. Simplified tools applied in Germany (including age, BMI, history of high blood glucose) [22] and Spain (including BMI, use of antihypertensive medication, history of high blood glucose) [25] were found to perform equally and better than the FINDRISC, respectively, in detecting undiagnosed T2DM. In the current study, three out of eight individual FINDRISC variables were significantly associated with undiagnosed T2DM (i.e. BMI, use of antihypertensive medication, history of high blood glucose), while two of those (i.e. BMI, history of high blood glucose) were significantly associated with dysglycaemia. In the original FINDRISC, the history of high blood glucose was the most powerful predictor of T2DM, whereas diet and physical activity components were included in the risk score to emphasize their importance, although they did not contribute much to the model's predictive power [19]. It should also be noted that the commonest missing item from the FINDRISC form in our study was WC, which is probably not frequently recognized as a risk factor for T2DM by the general population, as previously suggested [24]. Therefore, for rapid-screening purposes, a shorter, less time-consuming version of the FINDRISC, including the components most strongly associated with T2DM, may be preferable, while further validation studies are required to this direction.

Potential limitations of our study include the fact that although it is based on a community cohort, the results may not be applicable to the general population, especially in the case of HICs and the HICs under austerity measures, where vulnerable groups were targeted. Furthermore, only adults from the high-risk families were invited to take part in the

measurements, therefore our study population does not represent the whole background population, which might have effect on the diagnostic indicators. Moreover, the large study sample and design did not allow us to conduct OGTT, thus T2DM and prediabetes diagnosis were derived only by the use of FPG. However, this method has been also solely used in relevant studies assessing the diagnostic accuracy of the FINDRISC [20, 25], while in a recent study, 63% of people with undiagnosed T2DM and 62% of those with prediabetes were identified by using FPG [40]. Another limitation could be that the diagnosis was not confirmed by repeated glucose testing, but this condition is never fulfilled in epidemiological studies. On the other hand, the large and pan-European study sample can be considered as a major strength, while data were collected by well-trained researchers, following standardized protocols and procedures across all centers. Demographic characteristics and several socioeconomic data were also available in the current study, allowing us to further evaluate the FINDRISC in different vulnerable groups.

5. Conclusions

The results of the current study add to the available literature with data retrieved from vulnerable groups in a large-scale European cohort and provide novel information on the ability of the FINDRISC to identify individuals with T2DM and dysglycaemia that were unaware of their condition. Our data further support the use of the FINDRISC as a useful self-administrated tool and the first step in screening large multinational populations and identifying individuals primarily with undiagnosed T2DM but also with dysglycaemia. In the study population, a cut-off ≥14 found to be the most suitable value for identifying undiagnosed T2DM, while a cut-off ≥12 proved to be optimal for the detection of dysglycaemia. The different cut-offs identified for each country category could be also taken into consideration in the practical application, while the use of any simplified version of the FINDRISC could also be considered for systematic population screening. These findings could guide future public health actions to prioritize diabetes screening initiatives in vulnerable groups and tackle the health and social inequality-related issues.

Conflict of interest statement

None of the authors have any conflict to declare.

Authors' contribution

C.M. conducted the data analysis, interpretation and drafting of the manuscript. Y.M., CP.L., O.A. contributed to data analysis, interpretation and drafting of the manuscript. All authors have contributed in the study design, provided input, read and approved the manuscript.

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Table 1. Descriptive characteristics of the study population by country category

	Total sample (n=2,116)	**High-Income Countries** (Belgium-Finland) (n=610)	**High-Income Countries under austerity measures** (Greece-Spain) (n=1,074)	**Low/Middle-Income Countries** (Bulgaria-Hungary) (n=432)	P-value*
Age (years)	41.1 (5.48)	40.2 (5.58)[a]	42.3 (5.36)[a,b]	39.6 (4.97)[b]	<0.001
Females, % (n)	67.3 (1,425)	69.0 (421)[a,b]	62.6 (672)[a,c]	76.9 (332)[b,c]	<0.001
Occupation, % (n)					
Unemployed	5.1 (108)	2.5 (15)[a]	8.4 (90)[a,b]	0.7 (3)[b]	<0.001
Stay at home parent	12.5 (265)	7.5 (46)[a,b]	15.1 (162)[a]	13.2 (57)[b]	
Work part- time	11.6 (245)	15.9 (97)[a,b]	10.8 (116)[a]	7.4 (32)[b]	
Other [¥]	70.8 (1,498)	74.1 (452)[a]	65.7 (706)[a,b]	78.7 (340)[b]	
Educational level, % (n)					
<12 years	22.9 (485)	16.2 (99)[a]	27.1 (291)[a]	22.0 (95)	<0.001
≥12 years	77.1 (1,631)	83.8 (511)[a]	72.9 (783)[a]	78.0 (337)	
Smoking, % (n)					
Never	45.2 (957)	55.4 (338)[a,b]	43.2 (464)[a,c]	35.7 (155)[b,c]	<0.001
Ex-smoker	28.9 (611)	33.6 (205)[a,b]	27.6 (296)[a]	25.4 (110)[b]	
Current smoker	25.9 (548)	11.0 (67)[a,b]	29.2 (314)[a,c]	38.8 (167)[b,c]	
Undiagnosed T2DM, % (n)	1.2 (25)	1.0 (6)	1.1 (12)	1.6 (7)	0.620
Prediabetes, % (n)	5.6 (119)	8.0 (49)[a]	5.1 (55)	3.5 (15)[a]	0.019
FINDRISC value	10.2 (4.06)	10.5 (3.70)[a]	10.8 (3.70)[b]	8.35 (4.71)[a,b]	<0.001
FINDRISC categories, % (n)					
<7	16.4 (346)	12.6 (77)[a]	11.7 (126)[b]	33.1 (143)[a,b]	<0.001
7-11	47.7 (1010)	50.5 (308)[a]	48.9 (525)[b]	41.0 (177)[a,b]	
12-14	23.1 (488)	23.1 (141)	25.1 (270)[a]	17.8 (77)[a]	
15-20	12.4 (263)	13.4 (82)[a]	13.9 (149)[b]	7.4 (32)[a,b]	
>20	0.4 (9)	0.2 (2)	0.4 (4)	0.7 (3)	
FINDRISC components					
Age					
<45 years	76.0 (1,609)	80.2 (489)[a]	70.0 (752)[a,b]	85.2 (368)[b]	<0.001
45-54 years	23.1 (488)	19.0 (116)[a]	28.8 (309)[a,b]	14.6 (63)[b]	
55-64 years	0.8 (17)	0.5 (3)	1.2 (13)	0.2 (1)	
>64 years	0.1 (2)	0.3 (2)	0.0 (0)	0.0 (0)	
BMI					
<25kg/m^2	33.6 (710)	29.8 (182)[a]	30.4 (327)[b]	46.5 (201)[a,b]	<0.001
25-30kg/m^2	37.3 (789)	39.8 (243)[a]	38.5 (413)[b]	30.8 (133)[a,b]	
>30kg/m^2	29.2 (617)	30.3 (185)[a]	31.1 (334)[b]	22.7 (98)[a,b]	
Waist circumference					
F:<80cm, M:>94cm	13.7 (289)	7.4 (45)[a]	10.5 (113)[b]	30.3 (131)[a,b]	<0.001
F:80-88cm, M:94-102cm	33.6 (711)	32.1 (196)	34.9 (375)	32.4 (140)	
F:>88cm, M:>102cm	52.7 (1,116)	60.5 (369)[a]	54.6 (586)[b]	37.3 (161)[a,b]	

Physical activity (30min/day)					
Yes	63.4 (1,342)	71.1 (434)[a]	55.0 (591)[a,b]	73.4 (317)[b]	<0.001
No	36.6 (774)	28.9 (176)[a]	45.0 (483)[a,b]	26.6 (115)[b]	
Vegetables, fruit/berries consumption					
Every day	68.8 (1,456)	80.0 (493)[a]	58.7 (630)[a,b]	77.1 (333)[b]	<0.001
Not every day	31.2 (660)	19.2 (117)[a]	41.3 (444)[a,b]	22.9 (99)[b]	
Antihypertensive medication					
No	88.2 (1,867)	90.3 (551)[a]	90.9 (976)[b]	78.7 (340)[a,b]	<0.001
Yes	11.8 (249)	9.7 (59)[a]	9.1 (98)[b]	21.3 (92)[a,b]	
History of high blood glucose					
No	74.9 (1,584)	68.4 (417)[a,b]	75.7 (813)[a,c]	81.9 (354)[b,c]	<0.001
Yes	25.1 (532)	31.6 (193)[a,b]	24.3 (261)[a,c]	18.1 (78)[b,c]	
Family members with diabetes					
No	32.7 (691)	25.9 (158)[a,b]	33.1 (355)[a,c]	41.2 (178)[b,c]	<0.001
Grandparent, aunt, uncle or first cousin	39.6 (838)	40.2 (245)[a]	23.2 (249)[a]	21.5 (93)	
Parent, brother, sister or own child	27.7 (587)	33.9 (207)[a,b]	43.8 (470)[a]	37.3 (161)[b]	

Data are means (SD) except where noted otherwise.

Figures sharing the same superscript letters differentiate significantly from each other.

*_P_-values indicate the significance of the differences among country categories.

[¥] Other includes work full-time, full-time education and retired.

BMI: Body mass Index; FINDRISC: Finnish Diabetes Risk Score; F: females; M: males; T2DM: Type 2 diabetes mellitus

Table 2. Clinical characteristics of the study population by FINDRISC category

	FINDRISC 0-11 (n=1,356)	**FINDRISC 12-14** (n=488)	**FINDRISC 15-26** (n=272)	P-value*
FINDRISC value	7.96 (2.98)[a,b]	12.8 (0.82)[a]	16.7 (1.72)[b,c]	<0.001
Females, % (n)	67.5 (915)	63.3 (309)[a]	73.9 (201)[a]	0.012
Age (years)	40.6 (5.23)[a,b]	41.9 (5.41)[a]	42.4 (6.38)[b]	<0.001
Weight status, % (n)				
Underweight & Normal-weight	38.5 (522)[a,b]	11.9 (58)[a]	10.3 (28)[b]	<0.001
Overweight	36.8 (499)[a]	35.7 (174)[b]	26.5 (72)[a,b]	
Obese	24.7 (256)[a,b]	52.5 (256)[a,c]	63.2 (172)[b,c]	
Waist Circumference, % (n)				
F:<80cm, M:>94cm	30.5 (414)[a,b]	8.8 (43)[a]	4.8 (13)[b]	<0.001
F:80-88cm, M:94-102cm	28.8 (390)[a,b]	20.5 (100)[a,c]	13.2 (36)[b,c]	
F:>88cm, M:>102cm	40.7 (552)[a,b]	70.7 (345)[a,c]	82.0 (223)[b,c]	
Systolic BP (mmHg)	115.8 (16.2)[a,b]	120.5 (16.7)[a]	121.1 (17.0)[b]	<0.001
Diastolic BP (mmHg)	77.0 (11.0)[a,b]	80.3 (11.1)[a]	80.9 (12.1)[b]	<0.001
Fasting glucose (mmol/l)	5.15 (0.59)[a,b]	5.34 (0.88)[a,c]	5.55 (0.76)[b,c]	<0.001
Total cholesterol (mmol/l)	4.96 (0.94)[a,b]	5.10 (1.02)[a]	5.12 (0.97)[b]	0.002
LDL cholesterol (mmol/l)	3.05 (0.83)[a,b]	3.19 (0.89)[a]	3.22 (0.81)[b]	<0.001
HDL cholesterol (mmol/l)	1.41 (0.37)[a,b]	1.33 (0.33)[a]	1.30 (0.32)[b]	<0.001
Fasting Triglycerides (mmol/l)	1.09 (0.63)[a,b]	1.26 (0.71)[a]	1.31 (0.69)[b]	<0.001
Undiagnosed T2DM, % (n)	0.3 (4)[a,b]	1.4 (7)[a,c]	5.1 (14)[b,c]	<0.001
Prediabetes, % (n)	4.1 (56)[a,b]	7.0 (34)[a]	10.7 (29)[b]	<0.001

Data are means (SD) except where noted otherwise.

Figures sharing the same superscript letters differentiate significantly from each other.

**P*-values indicate the significance of the differences among FINDRISC categories: 0-11 (low and slightly elevated risk), 12-14 (moderate risk), 15-26 (high and very high risk)

BP: Blood pressure; FINDRISC: Finnish Diabetes Risk Score; F: females; M: males; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; T2DM: Type 2 diabetes mellitus

Table 3. Characteristics of FINDRISC using different cut-offs for detecting undiagnosed diabetes and dysglycaemia

	Total sample (n=2,116)				**High-Income Countries** (Belgium-Finland) (n=610)				**High-Income Countries under austerity measures** (Greece-Spain) (n=1,074)				**Low/Middle-Income Countries** (Bulgaria-Hungary) (n=432)			
Cut-off	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Se(%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**
Undiagnosed T2DM																
11	92.0	54.6	2.36	99.8	83.3	52.5	1.71	99.7	91.7	49.9	2.03	99.8	100	69.2	5.07	100.0
12	84.0	64.7	2.76	99.7	83.3	63.6	2.22	99.7	**83.3**	**61.1**	**2.36**	**99.7**	85.7	75.1	5.36	99.7
13	72.0	75.0	3.33	99.6	83.3	74.5	3.15	99.8	66.7	72.4	2.66	99.5	71.4	82.4	6.25	99.4
14	**68.0**	**81.7**	**4.26**	**99.5**	83.3	81.1	4.20	99.8	58.3	79.7	3.14	99.4	**71.4**	**87.8**	**8.77**	**99.5**
15	56.0	87.7	5.15	99.4	**83.3**	**86.9**	**5.95**	**99.8**	50.0	86.2	3.92	99.3	42.9	92.5	8.57	99.0
16	40.0	91.8	5.53	99.2	66.7	91.6	7.27	99.6	33.3	90.9	3.96	99.2	28.6	94.6	8.00	98.0
Dysglycaemia																
11	66.0	55.5	9.76	95.7	65.5	53.9	12.3	94.0	64.2	50.3	7.92	95.5	**72.7**	**70.2**	**11.6**	**98.0**
12	**58.3**	**65.7**	**11.1**	**95.6**	**54.5**	**64.8**	**13.3**	**93.5**	**59.7**	**62.0**	**9.46**	**95.9**	63.6	76.1	12.5	97.5
13	47.9	76.1	12.8	95.2	43.6	75.7	15.1	93.1	47.8	73.3	10.6	95.5	59.1	83.7	16.3	97.4
14	39.6	82.7	14.3	94.9	40.0	82.5	18.5	93.3	37.3	80.3	11.2	95.1	45.5	88.5	17.5	96.8
15	29.9	88.4	15.8	94.5	32.7	88.1	21.4	92.3	26.9	86.6	11.8	94.7	31.8	93.2	20.0	96.2
16	25.0	92.6	19.9	94.4	27.3	92.8	27.3	92.8	22.4	91.5	14.9	94.7	27.3	95.4	24.0	96.1

Data are percentages (%).

Figures in bold indicate optimal cut-offs.

FINDRISC: Finnish Diabetes Risk Score; T2DM: Type 2 diabetes mellitus; Se: sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value

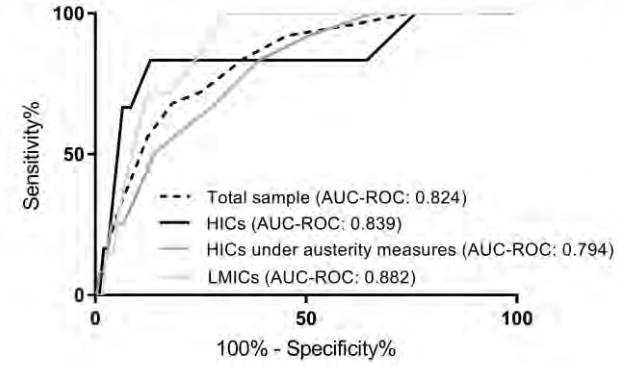
Table 4. Associations between the FINDRISC components and undiagnosed diabetes or dysglycaemia in the total sample (n=2,116)

	Undiagnosed T2DM		Dysglycaemia	
	OR	(95% CI)	OR	(95% CI)
Age				
Under 45 years	1.00		1.00	
Over 45 years	2.31	(0.97-5.48)	1.68	(1.14-2.47)
BMI				
<30kg/m^2	1.00		1.00	
>30kg/m^2	**2.82**	**(1.04-7.66)**	**1.80**	**(1.18-2.74)**
Waist circumference				
F:<88cm, M:<102cm	1.00		1.00	
F:>88cm, M:>102cm	1.48	(0.51-4.30)	1.35	(0.88-2.08)
Physical activity (30min/day)				
Yes	1.00		1.00	
No	0.65	(0.26-1.61)	0.91	(6.63-1.34)
Vegetables, fruit/berries consumption				
Every day	1.00		1.00	
Not every day	1.31	(0.54-3.17)	1.10	(0.75-1.62)
Antihypertensive medication				
No	1.00		1.00	
Yes	**2.63**	**(1.03-6.69)**	0.970	(0.58-1.62)
History of high blood glucose				
No	1.00		1.00	
Yes	**6.23**	**(2.57-15.1)**	**3.89**	**(2.60-5.83)**
Family members with diabetes				
No	1.00		1.00	
Grandparent, aunt, uncle or first cousin	1.13	(0.33-3.93)	0.99	(0.61-1.60)
Parent, brother, sister or own child	2.78	(1.00-7.74)	1.35	(0.88-2.06)

Multivariate logistic regression models adjusted for sex, educational level and country category.
BMI: Body mass Index; F: females; M: males; T2DM: Type 2 diabetes mellitus; OR: Odds Ratio; 95% CI: 95% Confidence interval

Figure 1. Receiver operating characteristic (ROC) curves for detecting (A) undiagnosed diabetes (B) dysglycaemia (AUC-ROC: Area under the ROC curve; HICs: High-income countries; LMICs: Low/middle-income countries)

A. ROC curves for undiagnosed diabetes by country category



B. ROC curves for dysglycaemia by country category