Association between prediabetes definition and progression to diabetes: the REDIA follow-up study

Norah Anthony, Victorine Lenclume, Adrian Fianu, Nathalie Le Moullec, Xavier Debussche, Patrick Gérardin, Catherine Marimoutou, Estelle Nobécourt

Diabetes Epidemiology and Management 3 (2021) 100024

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Original article

Association between prediabetes definition and progression to diabetes: The REDIA follow-up study

N. Anthony[a,b,c,*], V. Lenclume[b,c], A. Fianu[b,c], N.Le Moullec[c], X. Debussche[b,d], P. Gérardin[b,c], C. Marimoutou[a,b,c], E. Nobécourt[b,c,d,e]

[a] Methodological Support and Biostatistics Unit, University Hospital, Centre Hospitalier Universitaire de la Reunion, Saint-Denis, Reunion Island, France
[b] National Institute of Health and Medical Research (INSERM), Saint Pierre, Reunion Island CIC 1410, France
[c] University of La Réunion, University Hospital, Saint Denis, Reunion Island, France
[d] Diabetes and Endocrinology, Centre Hospitalier Max Querrien, Paimpol, France
[e] INSERM, DéTROI U1188, France

ARTICLE INFO

Article History:
Received 15 October 2021
Revised 31 October 2021
Accepted 3 November 2021
Available online 7 November 2021

Keywords:
Prediabetes
Type 2 diabetes mellitus
Secondary prevention
Screening

ABSTRACT

Aim To determine which prediabetes definition is the best predictor of progression to diabetes in Reunion Island where 10% of the population has treated diabetes.

Methods This follow-up study used data from the REDIA cross-sectional study, a population-based study conducted in two stages. Participants were enrolled in 1999–2001 (REDIA-1) and followed-up years later in 2006–2009 (REDIA-2). Odds ratios (OR) for prediabetes were estimated with their 95% confidence interval (95%CI) from logistic regression models. REDIA-1 participants with no previously identified diabetes in REDIA-1 were assessed for new pharmacologically treated diabetes in REDIA-2. We evaluated several biological definitions of prediabetes, each based on the combination of fasting plasma glucose (FPG), 2-h post-load plasma glucose (2hPG), and/or HbA1c: FPG-ADA (American Diabetes Association), FPG-WHO (World Health Organization), 2hPG, HbA1c-ADA, HbA1c-IEC (International Expert Committee), FPG-WHO/2hPG, and FPG-WHO/HbA1c-ADA.

Results A total of 432 participants met all inclusion criteria. Of these, 102 (23.6%) were classified as prediabetic using the FPG-WHO/2hPG definition, including 58 (56.9%) with isolated impaired glucose tolerance, 17 (16.6%) with isolated impaired fasting glucose, and 27 (26.5%) with both impairments. A total of 54 (12.5%) participants became treated diabetics and in descending order, the ORs for the FPG-WHO/2hPG, 2hPG, FPG-WHO, FPG-WHO/HbA1c-ADA, FPG-ADA, HbA1c-ADA, and HbA1c-IEC definitions were 6.96 [3.72–13.03], 5.91 [3.24–10.77], 5.82 [2.86–11.81], 4.68 [2.38–9.19], 4.37 [2.34–8.17], 3.24 [1.72–6.10], and 2.74 [1.32–5.70], respectively.

Conclusion The FPG-WHO/2hPG definition had the highest strength of association with the progression to treated diabetes, closely followed by the 2hPG and FPG-WHO definitions. Our findings highlight the importance of performing both FPG test and OGTT to diagnose prediabetes in primary care.

Introduction

In the last decades, diabetes has become a global epidemic and a major threat for populations [1]. New efforts combining research and public health interventions are welcome to improve the management of diabetes and to decrease its incidence [2,3].

One proven approach for the reduction of the diabetes disease burden is to focus public health interventions on prediabetes [4], a silent pathological stage between normoglycemia and diabetes. Subjects with prediabetes are at high risk of diabetes [5], with the ADA (American Diabetes Association) expert panel estimating that up to 70% will eventually become diabetic [6]. Several studies have shown that lifestyle interventions combining both improved nutrition and increased physical activity can reduce the progression from prediabetes to diabetes [7]. Since prediabetes is completely asymptomatic, affected subjects must be identified through routine screening in the primary care setting. So far, general practitioners (GPs) do not have access to a clear, standardized definition of prediabetes.

Indeed, there now coexist several biological definitions of prediabetes, the use of which depends on local health recommendations and clinical or epidemiological objectives. These definitions are based

* Corresponding author at: Methodological Support and Biostatistics Unit, University Hospital, Centre Hospitalier Universitaire de la Reunion, Saint-Denis, Reunion Island, France.
E-mail address: a-norah@hotmail.fr (N. Anthony).

https://doi.org/10.1016/j.deman.2021.100024

on the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or elevated glycated hemoglobin (HbA1c) levels - three metabolic abnormalities detected by measuring fasting plasma glucose (FPG), 2-h postload plasma glucose (2hPG) using the oral glucose tolerance test (OGTT), and HbA1c, respectively [8–10]. The cutoff values of FPG, 2hPG, and HbA1c used in current biological definitions of prediabetes are shown in Table 1. Since biological definitions of prediabetes moderately overlap and are not equally effective in predicting the progression to diabetes [11,12], discussions are ongoing regarding which should be favored. This is the case even in France, where the national health authority recommends screening for prediabetes using the FPG test or both FPG and OGTT. Public health interventions aimed at reducing the disease burden of diabetes should provide GPs with the definition of prediabetes that shows the best association.

To help identify the most useful definition of prediabetes, we reviewed data from the population-based study RÉunion DIAbetes (RÉDIA) [13], which was conducted in 1999–2001 and 2006–2009 in Reunion Island. This French overseas department located in the South-West Indian Ocean is of particular interest for two reasons. First, it is the French department with the highest prevalence of diabetes, with about 8% of Reunionese treated for diabetes [14,15]. Second, it is inhabited by a mixed population of European, African, and Asian origin [16,17]. Given these specificities, the probability of observing the progression to diabetes is higher in Reunion Island than in metropolitan France, and Reunionese are likely more representative of the global population.

The primary objective of the present study was to determine which definition of prediabetes is the best predictor of progression to diabetes in Reunion Island. The secondary objective was to identify factors associated with the progression to diabetes in the Reunionese population.

Material and methods

Study design

The population-based REDIA (RÉunion DIAbetes) study was conducted in two stages in Reunion Island. REDIA-1 (from May 1999 to September 2001) was a cross-sectional study aimed at identifying the clinical and behavioral factors associated with diabetes and its control in the multiethnic Reunionese population. REDIA-2 (from April 2006 to June 2009) was a follow-up study aimed at estimating the risk of health events among REDIA participants [13].

REDIA-1

The population and data collection of REDIA-1 have been described previously [18,19]. Briefly, the population was a random representative sample of 4610 Reunionese people aged 18–69 years (2017 men and 2593 women). Data were collected on demographic characteristics, clinical variables (medical history, treatments, and anthropometrics), lifestyle habits, and glycemic parameters (FPG, 2hPG, and HbA1c). The study was approved by the ethical committee of Montpellier [18], and informed written consent was obtained from all participants.

In the first phase of REDIA-1 (screening), clinical data were collected and capillary blood glucose (CBG) and HbA1c levels (*DCA 2000, Ames, Bayer Diagnostics, Basingstoke, England*) were measured in all participants. Participants were classified as having known diabetes (based on self-reporting), suspected diabetes, or normoglycemia. Suspected diabetes was defined by CBG levels ≥ 1.10 g/l (1.40 g/l if the person had not fasted) and/or HbA1c levels ≥ 6%. Overweight was defined as a body mass index (BMI) higher than or equal to 25 kg/m2 and obesity as a BMI higher than or equal to 30 kg/m2. Waist circumference was considered high when it exceeded 94 cm for men and 80 cm for women. In the second phase (check-up), the FPG test and the OGTT were performed in a balanced sample of participants with known diabetes, suspected diabetes, or normoglycemia (controls). Both tests were conducted using the glucose oxidase method.

REDIA-2

REDIA-2 follow-up took place seven years on average after participant enrollment in REDIA-1. Among the survivors eligible to follow-up, 624 refused to participate (overall participation rate of 83.3%). The same demographic characteristics, clinical variables, and anthropometrics were gathered as in REDIA-1 and some glycemic parameters were also measured but only in a sub-sample of participants.

Eligibility criteria

The criteria for inclusion in the present study were:

- not having been diagnosed or treated for diabetes (either pharmacological treatment and/or lifestyle modifications) at the time of REDIA-1 study;
- having no missing data on FPG, 2hPG, or HbA1c in REDIA-1;
- having no missing data on diabetes status in REDIA-2;

Study endpoints

Participants were classified as having normoglycemia, prediabetes, or diabetes based on the results of the HbA1c test conducted in the first phase of REDIA-1 and the results of the FPG test and the OGTT performed in the second phase of REDIA-1. Diagnosis of glycemic status was established using the glycemic parameter cutoff values shown in Table 1.

The evaluated definitions of prediabetes were: FPG-ADA, FPG-WHO (World Health Organization), 2hPG, HbA1c-ADA, HbA1c-IEC (International Expert Committee), FPG-WHO/2hPG, and FPG-WHO/HbA1c-ADA.

The primary outcome (diabetes status in REDIA-2) was being treated pharmacologically for a newly diagnosed diabetes at the time of REDIA-2 follow-up.

Table 1
Cutoff values of FPG, 2hPG, and HbA1c used in current biological definitions of prediabetes.

	Normoglycemia	Prediabetes	Diabetes
FPG (WHO)	FPG < 1.10 g/L (< 6.1 mmol/L)	IFG: FPG 1.10 - 1.25 g/L (6.1- 6.9 mmol/L)	FPG >= 1.26 g/L (>= 7 mmol/L)
2hPG	2hPG < 1.40 g/L (< 7.8 mmol/L)	IGT: 2hPG 1.40 - 1.99 g/L (7.8 – 11.0 mmol/L)	2hrPG >= 2 g/L (>= 11.1 mmol/L)
FPG (ADA)	FPG < 1.00 g/L (< 5.6 mmol/L)	IFG: FPG 1.00 - 1.25 g/L (5.6 - 6.9 mmol/L)	FPG >= 1.26 g/L (>= 7 mmol/L)
HbA1c (ADA)	HbA1c < 5.7%	HbA1c 5.7–6.4%	HbA1c >= 6.5%
HbA1c (IEC)	HbA1c < 6.0%	HbA1c 6.0–6.4%	HbA1c >= 6.5%

FPG: Fasting plasma glucose; WHO: World Health Organization; IFG: Impaired fasting glucose; 2hPG: 2-h postload plasma glucose; IGT: Impaired glucose tolerance; ADA: American Diabetes Association; HbA1c: Glycated hemoglobin; IEC: International Expert Committee.

The secondary outcome were clinical and lifestyle factors measured at REDIA-1.

Statistical analysis

The study sample was described using mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables.

For each definition of prediabetes, the strength of association between the study outcome and prediabetes was estimated using odds ratios (ORs) and 95% confidence intervals (95%CI). Normoglycemia was taken as reference category.

In a bivariate analysis, clinical and lifestyle factors associated with the progression from non-diabetes in REDIA-1 to diabetes in REDIA-2 were assessed using the Student's *t*-test or Mann-Whitney tests for quantitative variables and the chi-square test or Fisher's exact test for qualitative variables, as appropriate.

Finally, for each definition of prediabetes, the OR of the study outcome was estimated using a multivariate logistic regression model adjusted for the time interval between REDIA-1 and REDIA-2 for each participant and all factors with a p-value < 0.20 in the bivariate analysis. Only the factors associated with a p-value <0.05 after a backward stepwise procedure were retained in the final model. All these analyses were performed in R version 4.0.0.

Results

Definition of prediabetes which has the highest strength of association with the progression to diabetes

A total of 432 REDIA participants met the inclusion criteria for the present study (Fig. 1). Of these, 269 (62.3%) were female and 163 (37.7%) were male. Mean age was 46.4 (11.6) years. Obesity was found in 21.3% of participants, and an elevated waist circumference was observed in 47.9% of men and 75.7% of women. A first-degree family history of diabetes was found in 54.3% of participants and a history of treated high blood pressure in 19.4% of them. A large majority of participants reported being physically active, 80.7% moderate to very high daily professional or domestic physical activity and 43.6% sport activity (Table 2). A total of 54 (12.5%) subjects were pharmacologically treated for diabetes at the time of the REDIA-2 follow-up, which met our primary outcome. Depending on the definition that was evaluated, the prevalence of prediabetes ranged from 10.2% (FPG-WHO definition) to 34.3% (FPG-ADA definition). For instance, the FPG-WHO/2hPG definition identified 102 (23.6%) participants with prediabetes, including 58 (56.9%) with isolated IGT, 17 (16.6%) with isolated IFG, and 27 (26.5%) with both IGT and IFG (Table 3).

Whatever the definition used, subjects with prediabetes had a significantly higher risk of progressing to diabetes compared to

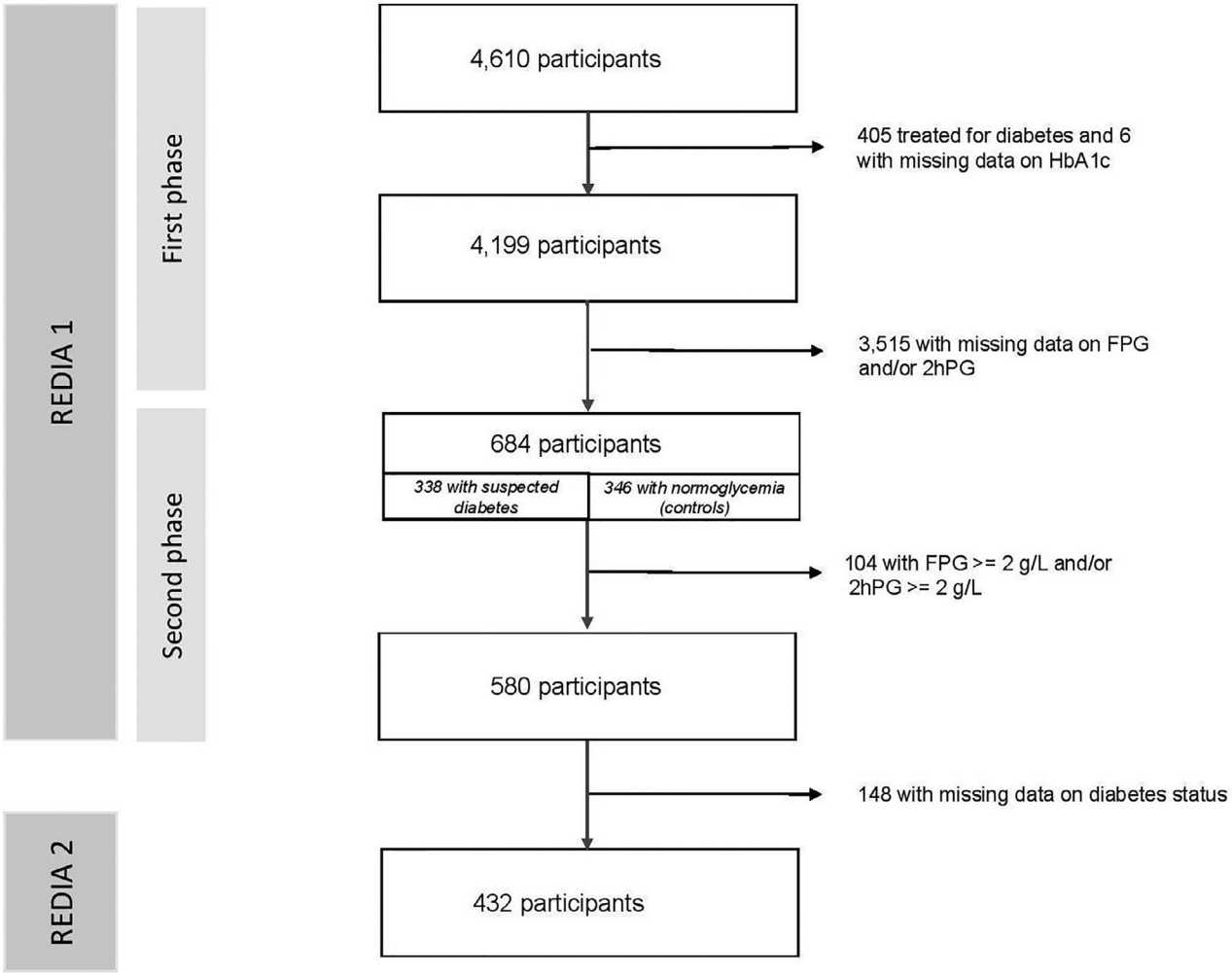

Fig. 1. flowchart of participant inclusion
HbA1c: Glycated hemoglobin; FPG: Fasting plasma glucose; 2hPG: 2-h postload plasma glucose.

Table 2
Baseline characteristics of the 432 included subjects.

	Total (*N* = 432) N (%) or *mean ± SD
Sex (female/male)	269/163 (62.3/37.7)
Age (years)	46.4 ± 11.6*
History of treated high blood pressure	84 (19.4)
BMI (kg/m²)	
<25	187 (43.3)
[25−30[	153 (35.4)
>=30	92 (21.3)
Waist circumference (cm)	91.4 ± 12.6*
Missing	*1*
Waist circumference in men (cm)	
< 94	85 (52.1)
>= 94	78 (47.9)
Waist circumference in women (cm)	
< 80	65 (24.3)
>= 80	203 (75.7)
Family history of diabetes	
Missing	*5*
None	161 (37.7)
Yes, second-degree or more distant	34 (8.0)
Yes, first-degree	232 (54.3)
Smoking status	
Current smoker	74 (17.1)
Former smoker	74 (17.1)
Never smoked	284 (65.7)
Daily professional or domestic physical activity	
Missing	*1*
Low	83 (19.3)
Moderate to very high	348 (80.7)
Sport activity	188 (43.6)

BMI: Body mass index.

normoglycemic subjects. In descending order, the crude (unadjusted) ORs of diabetes for the FPG-WHO/2hPG, 2hPG, FPG-WHO, FPG-WHO/HbA1c-ADA, FPG-ADA, HbA1c-ADA, and HbA1c-IEC definitions were 6.96 [95%CI: 3.72−13.03], 5.91 [3.24−10.77], 5.82 [2.86−11.81], 4.68 [2.38−9.19], 4.37 [2.34−8.17], 3.24 [1.72−6.10], and 2.74 [1.32−5.70], respectively (Fig. 2). Considering the FPG-WHO/2hPG definition which is associated with the highest risk of developing diabetes, 31 (43.7%) of REDIA-1 prediabetics became treated diabetics at REDIA-2.

Table 3
Classification of the 432 included subjects into normoglycemia, prediabetes, and diabetes based on current biological definitions of prediabetes.

	Total (*N* = 432) *N (%)*
FPG-ADA	
Normoglycemia	276 (63.9)
Prediabetes	156 (36.1)
FPG-WHO	
Normoglycemia	380 (88.0)
Prediabetes	52 (12.0)
2hPG	
Normoglycemia	341 (78.9)
Prediabetes	91 (21.1)
HbA1c-ADA	
Normoglycemic	277 (64.1)
Prediabetes	135 (31.2)
Diabetes *(newly diagnosed)*	20 (4.6)
HbA1c-IEC	
Normoglycemic	357 (82.6)
Prediabetes	55 (12.7)
Diabetes *(newly diagnosed)*	20 (4.6)
FPG-WHO/2hPG	
Normoglycemic	322 (74.5)
Prediabetes	102 (23.6)
Diabetes *(newly diagnosed)*	8 (1.9)
FPG-WHO/HbA1c-ADA	
Normoglycemic	267 (61.8)
Prediabetes	141 (32.6)
Diabetes *(newly diagnosed)*	24 (5.6)

FPG: Fasting plasma glucose; ADA: American Diabetes Association; WHO: World Health Organization; 2hPG: 2-h postload plasma glucose; HbA1c: Glycated hemoglobin; IEC: International Expert Committee.

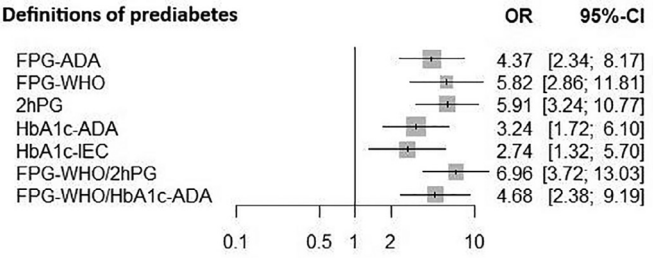

Fig. 2. Definitions of prediabetes and risk of progression to diabetes
OR: Odds ratio; CI: Confidence Interval. FPG: Fasting plasma glucose; ADA: American Diabetes Association; WHO: World Health Organization; 2hPG: 2-h postload plasma glucose; HbA1c: Glycated hemoglobin; IEC: International Expert Committee.

Clinical factors associated with the progression to diabetes

Subjects who were pharmacologically treated for diabetes in REDIA-2 had significantly higher BMI ($p = 0.001$), waist circumference ($p<0.001$), first-degree family history of diabetes ($p < 0.001$), and history of treated high blood pressure ($p = 0.017$) than the rest of the study population (Table 4). However, lower levels of daily professional or domestic physical activity as lack of sports activity were not associated with the risk for progression to diabetes.

After the backward stepwise procedure, adjusted ORs for the different definitions of prediabetes were consistent with unadjusted ORs (Appendix A). Note that since BMI and waist circumference are correlated, only BMI was included in the model to avoid multicollinearity.

Discussion

In our study, the FPG-WHO/2hPG prediabetes definition had the highest association in predicting the progression to diabetes over an average of 7 years, followed by the 2hPG and FPG-WHO definitions. This finding suggests that performing the OGTT in addition to the FPG test (using WHO cutoff values) greatly improves the detection of individuals at risk of diabetes. In fact, individuals with isolated IGT accounted for the majority of subjects in our sample (56.9%), meaning that performing the FPG test alone would result in missing more than half of prediabetes cases in Reunion Island. It is also important to note that according to the FPG-WHO/2hPG definition, about 43.7 of prediabetics became diabetic seven years later on average and similar findings are found in the literature [20,21].

The determinants that were statistically associated with the progression to diabetes were family history of diabetes, history of treated high blood pressure, BMI, and waist circumference. It is reassuring to note that these determinants are those found in the clinical score FINDRISC, recommended in France to identify subjects at risk of developing diabetes [22]. Unfortunately, despite the National Health Authority recommendation, the FINDRISC is neither widely known nor used by GPs in Reunion Island [23].

Diabetes is also a major public health concern in Mauritius, Reunion's neighboring island [24,25], whose population is characterized by similar ethnic diversity and nutritional habits (mainly originating in India) as the Reunionese population. In line with our findings, a longitudinal population-based study carried out in Mauritius found IGT to be a better predictor of diabetes than IFG [26]. Another study conducted in Mauritius found IGT to be more prevalent than IFG, with a higher proportion of women having isolated IGT and a higher proportion of men having isolated IFG [27]. This latter finding is of

Table 4
Factors associated with being pharmacologically treated for diabetes in REDIA-2, *N* = 432.

	Not pharmacologically treated for diabetes in REDIA-2 (*N* = 378) *N (%)*	Pharmacologically treated for diabetes in REDIA-2 (*N* = 54) *N (%)*	Total (*N* = 432) *N (%)*	p
Sex (female/male)	233/145 (61.6/38.4)	36/18 (66.7/33.3)	269/163 (62.3/37.7)	0.476
Age (years)	46.1 ± 11.8*	48.4 ± 9.9	46.4 ± 11.6	0.173
History of treated high blood pressure	67 (17.7)	17 (31.5)	84 (19.4)	**0.017**
BMI (kg/m^2)				**0.001**
<25	173 (45.8)	14 (25.9)	187 (43.3)	
[25−30[	134 (35.4)	19 (35.2)	153 (35.4)	
>=30	71 (18.8)	21 (38.9)	92 (21.3)	
Waist circumference (cm)	90.3 ± 12.5	98.4 ± 11.5	91.4 ± 12.6	**<0.001**
Missing	*1*	*0*	*1*	
Family history of diabetes				**<0.001**
Missing	3	2	5	
None	151 (40.3)	10 (19.2)	161 (37.7)	
Yes, second-degree or more distant	33 (8.8)	1 (1.9)	34 (8.0)	
Yes, first-degree	191 (50.9)	41 (78.8)	232 (54.3)	
Smoking status				0.545
Current smoker	67 (17.7)	7 (13.0)	74 (17.1)	
Former smoker	66 (17.5)	8 (14.8)	74 (17.1)	
Never smoked	245 (64.8)	39 (72.2)	284 (65.7)	
Daily professional or domestic physical activity				0.105
Missing	*1*	*0*	*1*	
Low	77 (20.4)	6 (11.1)	83 (19.3)	
Moderate to very high	300 (79.6)	48 (88.9)	348 (80.7)	
Sport activity	168 (44.6)	20 (37.0)	188 (43.6)	0.297

BMI: Body mass index. * Mean ± SD.

particular interest, as treated diabetes is more prevalent in women than men in Reunion Island [15], further highlighting the importance of performing both the FPG test and the OGTT when screening for prediabetes.

At present, the French Health Authority recommends screening for prediabetes and diabetes using the FPG test alone or in combination with the OGTT. In practice, however, the OGTT is rarely performed. In a recent study conducted in Reunion Island in primary care, many GPs were unaware of official recommendations for prediabetes screening and/or did not know the 2hPG-based definition of prediabetes. They therefore used the OGTT only marginally [23]. This suggests that the prevalence of IGT is widely underestimated in Reunion Island.

From a public health perspective, failure to use the OGTT for the screening of prediabetes is counterproductive because individuals with isolated IGT have been shown to be more receptive to lifestyle interventions than those with isolated IFG [28]. Since individuals with isolated IGT are the best target for preventive actions to reduce the diabetes burden, GPs should clearly be encouraged to use the OGTT.

Some significant disadvantages of using the FPG-WHO/2hPG definition must nevertheless be acknowledged. First, combining the FPG test with the OGTT is not the most efficient approach for the screening of prediabetes [29]. In the context of population-based screening, the decision to use this less efficient strategy should be made based on available resources. Second, subjects screened using this strategy are not only required to fast prior to taking the FPG test, but must also wait at least 2 h in the laboratory while taking the OGTT. To this is added the fact that minor side effects after glucose uptake during the OGTT have been reported [30]. Interestingly, some researchers have raised the possibility of using 1-h postload plasma glucose instead of 2hPG to increase acceptability of the OGTT [31]. Another disadvantage of the FPG-WHO/2hPG definition is the relatively high intra-individual variability over time of FPG and 2hPG levels compared to HbA1c levels [32]. Indeed, HbA1c reflects plasma glucose levels for the preceding three months, whereas FPG and 2hPG are glycemic values at a given time. To this is added the fact that the HbA1c test is easier to perform than OGTT. Yet, in France, the HbA1c test is recommended only for the monitoring of patients with diagnosed diabetes and still not for diagnosis. Importantly, in our sample, HbA1c-based definitions of prediabetes were the least effective in predicting the progression to diabetes, and adding the HbA1c-ADA definition to the FPG-WHO definition did not increase predictive performance. In short, while the HbA1c test is easy to perform and yields more reproducible results than the FPG test and the OGTT, our results suggest that it is less effective in detecting subjects at risk of diabetes. In fact, several studies have documented a low concordance between HbA1c levels and 2hPG levels, which is likely explained by the fact that these two parameters identify different risk profiles [33−35].

Conflicting results have been reported regarding the effectiveness of HbA1c-based definitions in predicting the progression to diabetes. Both an individual participant data meta-analysis and a Cochrane meta-analysis found these definitions to have a better predictive value than our study did [36,37]. In both meta-analyses, however, the outcome was diabetes defined based on a combination of self-reporting, measures of glycemic parameters (FPG, 2hPG, and HbA1c), and/or use of anti-diabetic drugs. Using HbA1c to define both baseline prediabetes and the study outcome is problematic as a positive correlation is expected between these two HbA1c values. In fact, it has been demonstrated that due to hemoglobin glycation acceleration [38], HbA1c levels increase with age independently of plasma glucose levels [35,39]. Since HbA1c levels tend to increase following the diagnosis of prediabetes and because of aging, using current HbA1c-based definitions likely results in overestimating the risk of progression to diabetes. In view of this, age-appropriate HbA1c cutoff values may be needed for the diagnosis of prediabetes and diabetes. Finally, ethnicity has been shown to impact the predictive performance of HbA1c-based definitions of prediabetes, with HbA1c levels being higher in non-whites independently of plasma glucose values [40,41]. This could explain the lower strength of association of HbA1c-based definitions in our multiethnic population.

A recent meta-analysis assessed the predictive value of definitions of prediabetes for other outcomes, including all-cause mortality, cardiovascular disease, coronary heart disease, and stroke. The FPG-

WHO/2hPG and 2hPG definitions were found to have higher predictive value than HbA1c-based definitions [42]. Though diabetes was defined in our study based on the use of pharmacological treatment, the consistency of our results with those of this meta-analysis supports the interest of using the OGTT for prediabetes screening.

In our study, several limitations can be cited. First, from a statistical perspective, ORs parameters were used instead of relative risks or hazard ratios because time intervals between REDIA-1 and REDIA-2 fluctuated for each participant who were only seen at two times (and not followed between) and the precise date of diabetes diagnosis was not documented. In fact, the REDIA survey is more a succession of two cross-sectional studies rather than a longitudinal study. Second, since the prevalence of the primary outcome was quite high (12.5% participants of the study developed diabetes as defined in the method section), ORs might slightly overestimate the real relative risks. However and despite of this, it is important to emphasize that the two biological definitions which include 2hPG have the confidence interval with the highest lower limit. This is consistent with the fact that a majority of prediabetics can be diagnosed only with OGTT. Finally, it can be noted that the sample of our study is mostly made up of women (62.3%) as is common in health surveys. However, diabetes in Reunion Island affects more women [15] and therefore it seems unlikely that the over-representation of women in the sample biases the main result.

The main strength of our study is that it is one of the few to look at the respective associations of currently used definitions of prediabetes with diabetes occurrence in a sample composed mainly of mixed-race individuals.

In order to improve the detection of subjects at risk of diabetes while ensuring high acceptability of prediabetes screening in the population, a strategy combining the FINDRISC, the FPG test, and the OGTT could be implemented. In this strategy, subjects with a high FINDRISC would first be offered the FPG test, and those with a high FINDRISC and normal FPG levels would then be offered the OGTT. The effectiveness of this strategy, which would have to be evaluated, would require better communication on the interest of using the FINDRISC routinely in primary care.

In conclusion, all definitions of prediabetes evaluated in our study were able to predict the progression to diabetes in Reunion Island. The FPG-WHO/2hPG definition had the highest association, followed by the 2hPG and FPG-WHO definitions. Our study also found that using the FPG test alone would result in missing more than half of prediabetes cases in the Reunionese population. These findings suggest that better communication on the importance of using both the FPG test and the OGTT for the screening of prediabetes could considerably reduce the burden of diabetes. While this strategy is clearly needed in Reunion Island, where the prevalence of diabetes is especially high, we believe it would likely also be effective in other multi-ethnic populations.

Declaration of Competing Interest

None of the authors had any conflict of interest.

Funding

This project is co-financed by the European Union and the Regional Council of Réunion.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.deman.2021.100024.

References

[1] Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2•7 million participants. Lancet 2011;378:31–40. doi: 10.1016/S0140-6736(11)60679-X.
[2] Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the diabetes prevention program outcomes study. Lancet Diabetes Endocrinol 2015;3:866–75. doi: 10.1016/S2213-8587(15)00291-0.
[3] Lindström J, Peltonen M, Eriksson JG, Aunola S, Hämäläinen H, Ilanne-Parikka P, et al. Determinants for the effectiveness of lifestyle intervention in the finnish diabetes prevention study. Diabetes Care 2008;31:857–62. doi: 10.2337/dc07-2162.
[4] Zand A, Ibrahim K, Patham B. Prediabetes: why should we care? Methodist Debakey Cardiovasc J 2018;14:289–97. doi: 10.14797/mdcj-14-4-289.
[5] Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012;379:2279–90. doi: 10.1016/S0140-6736(12)60283-9.
[6] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–9. doi: 10.2337/dc07-9920.
[7] Glechner A, Keuchel L, Affengruber L, Titscher V, Sommer I, Matyas N, et al. Effects of lifestyle changes on adults with prediabetes: a systematic review and meta-analysis. Prim Care Diabetes 2018;12:393–408. doi: 10.1016/j.pcd.2018.07.003.
[8] International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–34. doi: 10.2337/dc09-9033.
[9] World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia : report of a WHO/IDF consultation. World Health Organization; 2006 https://apps.who.int/iris/handle/10665/43588.
[10] American Diabetes Association. Understanding A1C - Diagnosis. https://www.diabetes.org/a1c/diagnosis (accessed August 31, 2021).
[11] Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, et al. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol 2017;5:34–42. doi: 10.1016/S2213-8587(16)30321-7.
[12] Gonzalez A, Deng Y, Lane AN, Benkeser D, Cui X, Staimez LR, et al. Impact of mismatches in HbA1c vs glucose values on the diagnostic classification of diabetes and prediabetes. Diabet Med 2020;37:689–96. doi: 10.1111/dme.14181.
[13] https://www.santepubliquefrance.fr/content/download/55663/file/rapport-redia.pdf.
[14] Santé Publique France. http://beh.santepubliquefrance.fr/beh/2017/27-28/2017_27-28_3.html.
[15] ORS OI 2020. Le diabète et les personnes diabétiques à La Réunion. Chiffres clés – Edition 2020. https://www.lareunion.ars.sante.fr/chiffre-cles-2020-le-diabete-et-les-personnes-diabetiques-la-reunion
[16] Dubut V, Murail P, Pech N, Thionville M-D, Cartault F. Inter- and extra-Indian admixture and genetic diversity in reunion island revealed by analysis of mitochondrial DNA. Ann Hum Genet 2009;73:314–34. doi: 10.1111/j.1469-1809.2009.00519.x.
[17] Médéa L. La construction identitaire dans la société réunionnaise. J Anthropol 2003;n° 92-93:261–81.
[18] Favier F, Jaussent I, Moullec NL, Debussche X, Boyer MC, Schwager JC, et al. Prevalence of Type 2 diabetes and central adiposity in La Reunion Island, the REDIA Study. Diabetes Res Clin Pract 2005;67:234–42. doi: 10.1016/j.diabres.2004.07.013.
[19] Cournot M, Lenclume V, Le Moullec N, Debussche X, Doussiet E, Fagot-Campagna A, et al. Prevalence, treatment and control of hypertension in La Réunion: the RÉDIA population-based cohort study. Blood Press 2017;26:39–47. doi: 10.1080/08037051.2016.1182854.
[20] Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–73. doi: 10.2337/dc09-1939.
[21] Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract 2007;78:305–12. doi: 10.1016/j.diabres.2007.05.004.
[22] Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care 2003;26:725–31. doi: 10.2337/diacare.26.3.725.
[23] Montée N., Anthony N., Collet A., Franco J.-.M., Marimoutou C., Leruste S., et al. Knowledge, attitudes and practices regarding prediabetes among general practitioners in Reunion Island (FORTHCOMING) n.d.
[24] Magliano DJ, Söderberg S, Zimmet PZ, Chen L, Joonas N, Kowlessur S, et al. Explaining the Increase of Diabetes Prevalence and Plasma Glucose in Mauritius. Diabetes Care 2012;35:87–91.
[25] Söderberg S, Zimmet P, Tuomilehto J, de Courten M, Dowse GK, Chitson P, et al. Increasing prevalence of Type 2 diabetes mellitus in all ethnic groups in Mauritius. Diabet Med 2005;22:61–8. doi: 10.1111/j.1464-5491.2005.01366.x.
[26] Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, et al. Impaired fasting glucose or impaired glucose tolerance. What best predicts future diabetes in Mauritius? Diabetes Care 1999;22:399–402. doi: 10.2337/diacare.22.3.399.

[27] Williams JW, Zimmet PZ, Shaw JE, de Courten MP, Cameron AJ, Chitson P, et al. Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? Diabet Med 2003;20:915–20. doi: 10.1046/j.1464-5491.2003.01059.x.
[28] Campbell MD, Sathish T, Zimmet PZ, Thankappan KR, Oldenburg B, Owens DR, et al. Benefit of lifestyle-based T2DM prevention is influenced by prediabetes phenotype. Nat Rev Endocrinol 2020;16:395–400. doi: 10.1038/s41574-019-0316-1.
[29] Zhang P, Engelgau MM, Valdez R, Benjamin SM, Cadwell B, Narayan KMV. Costs of screening for pre-diabetes among US adults: a comparison of different screening strategies. Diabetes Care 2003;26:2536–42. doi: 10.2337/diacare.26.9.2536.
[30] NHANES. Oral Glucose Tolerance Test (OGTT). https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/OGTT_H.htm
[31] Bergman M, Manco M, Sesti G, Dankner R, Pareek M, Jagannathan R, et al. Petition to replace current OGTT criteria for diagnosing prediabetes with the 1-h post-load plasma glucose ≥ 155 mg/dl (8.6 mmol/L). Diabetes Res Clin Pract 2018;146:18–33. doi: 10.1016/j.diabres.2018.09.017.
[32] Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes Care 2011;34:S184–90. doi: 10.2337/dc11-s216.
[33] Chatzianagnostou K, Vigna L, Di Piazza S, Tirelli AS, Napolitano F, Tomaino L, et al. Low concordance between HbA1c and OGTT to diagnose prediabetes and diabetes in overweight or obesity. Clin Endocrinol (Oxf) 2019;91:411–6. doi: 10.1111/cen.14043.
[34] Dong XL, Liu Y, Sun Y, Sun C, Fu FM, Wang SL, et al. Comparison of HbA1c and OGTT criteria to diagnose diabetes among Chinese. Exp Clin Endocrinol Diabetes 2011;119:366–9. doi: 10.1055/s-0030-1267183.
[35] Kim CH, Kim HK, Kim BY, Jung CH, Mok JO, Kang SK. Impact of hemoglobin A1c-based criterion on diagnosis of prediabetes: the Korea national health and nutrition examination survey 2011. J Diabetes Investig 2015;6:51–5. doi: 10.1111/jdi.12245.
[36] Lee CMY, Colagiuri S, Woodward M, Gregg EW, Adams R, Azizi F, et al. Comparing different definitions of prediabetes with subsequent risk of diabetes: an individual participant data meta-analysis involving 76 513 individuals and 8208 cases of incident diabetes. BMJ Open Diabetes Res Care 2019;7. doi: 10.1136/bmjdrc-2019-000794.
[37] Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. Cochrane Database Syst Rev 2018. doi: 10.1002/14651858.CD012661.pub2.
[38] Nakashima K, Nishizaki O, Andoh Y. Acceleration of hemoglobin glycation with aging. Clin Chim Acta 1993;215:111–8. doi: 10.1016/0009-8981(93)90254-2.
[39] Pani LN, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the framingham offspring study and the national health and nutrition examination survey 2001-2004. Diabetes Care 2008;31:1991–6. doi: 10.2337/dc08-0577.
[40] Cavagnolli G, Pimentel AL, Freitas PAC, Gross JL, Camargo JL. Effect of ethnicity on HbA1c levels in individuals without diabetes: systematic review and meta-analysis. PLoS ONE 2017;12:e0171315. doi: 10.1371/journal.pone.0171315.
[41] Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. Diabetes Res Clin Pract 2010;87:415–21. doi: 10.1016/j.diabres.2009.12.013.
[42] Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ 2020;370. doi: 10.1136/bmj.m2297.

Appendix A

Risk of progression to diabetes according to definition of prediabetes: non-adjusted and adjusted odds ratios.

Definition of prediabetes	Non-adjusted ORs	Adjusted ORs*
FPG-ADA	4.37 [2.34; 8.17]	5.19 [2.66;10.61]
FPG-WHO	5.82 [2.86; 11.81]	5.46 [2.51;11.81]
2hPG	5.91 [3.24; 10.77]	5.89 [3.09;11.37]
HbA1c-ADA	3.24 [1.72; 6.10]	2.58 [1.30;5.16]
HbA1c-IEC	2.74 [1.32; 5.70]	2.23 [0.96;4.88]
FPG-WHO/2hPG	6.96 [3.72; 13.03]	6.99 [3.59;13.96]
FPG-WHO/HbA1c-ADA	4.68 [2.38; 9.19]	4.29 [2.14;8.97]

* OR were adjusted for time intervals between REDIA-1 and REDIA-2, age, history of high blood pressure, BMI, and familial history of diabetes.
OR: Odds ratio; FPG: Fasting plasma glucose; ADA: American Diabetes Association; WHO: World Health Organization; 2hPG: 2-h postload plasma glucose; HbA1c: Glycated hemoglobin; IEC: International Expert Committee.