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Reproducibility of a prediabetes classification in a contemporary population

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ABSTRACT

Aims: To assess whether meeting both fasting plasma glucose (FPG) and HbA1c criteria for prediabetes in people at high risk indicates with near certainty the presence of dysglycemia on repeat testing.
Methods: Observational study using data from Vitamin D and Type 2 Diabetes (D2d) study. HbA1c, FPG were measured at screening visit 1; FPG, HbA1c and 2 h plasma glucose (2hPG) measured at screening visit 2 (a median of 21 days later); participants classified as having normal glucose regulation (all 3 tests in normal range), prediabetes or diabetes (at least 1 of 3 tests in diabetes range). A predictive model was developed to estimate the probability of confirming dysglycemia and for detecting diabetes at screening visit 2 based on values of FPG and HbA1c at screening visit 1.
Results: Of 1271 participants who met both FPG and HbA1c criteria for prediabetes at screening visit 1, 98.6% exhibited dysglycemia (defined as prediabetes or diabetes) on repeat testing (84.5% were classified as having prediabetes, 14.1% were reclassified as having diabetes). Of those with diabetes, 62.6% were identified by 2hPG alone.
Conclusions: Combined measurement of FPG and HbA1c is a reliable and reproducible measure to identify presence of dysglycemia among people at high risk. A prediction model is provided to help clinicians decide whether an oral glucose tolerance test will provide value in detecting diabetes based on the 2hPG criterion.

1. Introduction

Prediabetes, defined as having blood glucose levels above normal but below diabetes thresholds, is a risk state associated with developing diabetes. The definition of prediabetes by the American Diabetes Association (ADA) is based on meeting any one

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of the following laboratory criteria: fasting plasma glucose (FPG) from 100 to 125 mg/dL (5.6–6.9 mmol/L), hemoglobin A1c (HbA1c) from 39 to 46 mmol/mol (5.7–6.4%) or 2-h plasma glucose (2hPG) after a 75 g glucose load from 140 to 199 mg/dL (7.8–11.0 mmol/L) and not meeting any criteria for diabetes [1]. According to the ADA, these criteria can be assessed once to define prediabetes and do not require confirmation [1].

Any of the three glycemic criteria can be used individually to identify prediabetes; however, the FPG and HbA1c are the most commonly obtained tests in the clinical setting. The 2hPG value is rarely assessed because it requires a 75-g oral glucose tolerance test (OGTT), which is burdensome and costly. Data on the utility of using both FPG and HbA1c criteria to identify prediabetes and the value of confirmatory testing with an OGTT to evaluate the 2hPG criterion are lacking. In cross-sectional analyses of the National Health and Nutrition Examination Survey (NHANES), when FPG, HbA1c and 2hPG were measured simultaneously, 6.9% of persons who met the HbA1c or the FPG criterion for prediabetes also met diabetes criteria based on the 2hPG value [2]. Among those that met both FPG and HbA1c criteria for prediabetes, 14.2% also met the 2hPG criterion for diabetes.

The present study is a secondary analysis of data from the Vitamin D and Type 2 Diabetes (D2d) Study a large U.S.-based diabetes prevention trial that employed FPG and HbA1c concurrently for the initial identification of people with prediabetes, followed by repeat evaluation with FPG and HbA1c and an OGTT to assess the 2hPG criterion. Therefore, D2d provides a rare opportunity to assess the reproducibility of the biochemical testing and the value of confirmatory testing that includes an OGTT when both FPG and HbA1c criteria are concurrently in the prediabetes range.

2. Subjects, materials, and methods

2.1. Overview of the D2d study and population

D2d is a multicenter (22 clinical sites in the U.S.), randomized, double-blind, placebo-controlled, parallel-group, primary prevention clinical trial comparing the effects of vitamin D vs. placebo in people with prediabetes who are followed for incident diabetes. The design of D2d has been published [3]. The study (ClinicalTrials.gov Identifier NCT01942694) is approved and monitored by an independent Data and Safety Monitoring Board and the Institutional Review Board of each collaborating clinical site, and all participants provided informed consent.

Eligible participants for the trial had to meet any two or all three of the glycemic criteria for prediabetes established by the ADA in 2010: FPG 100–125 mg/dL (5.6–6.9 mmol/L), HbA1c 5.7–6.4% (39–46 mmol/mol) or 2hPG after a 75-g glucose load 140–199 mg/dL (7.8–11.0 mmol/L), and not meet any criteria for diabetes [4]. Other entry criteria included age ≥30 years (≥25 years for American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders) and BMI of 24–42 kg/m^2 (22.5–42 kg/m^2 for Asian Americans). Exclusion criteria relevant to the present analysis include hemoglobin variants (detected at screening) that affect measurement of HbA1c [5], use of medications approved for treatment of diabetes, bariatric surgery and chronic kidney disease (eGFR < 50 mL/min per 1.73 m^2) [3].

2.2. Derivation of the present cohort

In-person screening was performed in two steps (Supplemental Fig. 1). At screening visit 1, non-glycemic eligibility criteria for the trial (e.g., medical history, laboratory tests for safety) were confirmed and glycemic criteria for prediabetes were evaluated by measuring FPG and HbA1c either at the site's local laboratory or the D2d Central Laboratory. Algorithms utilizing the FPG and HbA1c results from screening visit 1 provided individual sites with guidance as to which participants should proceed to screening visit 2. While the D2d site-specific algorithms allowed certain participants who had FPG or HbA1c outside the prediabetes range at screening visit 1 to proceed to the next screening visit, the present analysis excludes those participants. At screening visit 2, which occurred a median of 21 days (range 14–29 days) later, a 75-g OGTT was performed and 2hPG, along with repeated FPG and HbA1c, were analyzed by the D2d central laboratory to determine final eligibility for the trial. The present analysis is limited to participants (n = 1271) who met both FPG and HbA1c prediabetes criteria at screening visit 1 and had both the screening visit 1 and screening visit 2 tests analyzed by the D2d Central Laboratory to eliminate the influence of analytical variability among laboratories. Hemoglobin A1c was measured with the use of an ion-exchange high-performance liquid chromatography method certified by the National Glycohemoglobin Standardization Program [3]. Plasma glucose was measured with the use of a hexokinase method.

2.3. Data analysis

2.3.1. Reproducibility of FPG and HbA1c

For each participant, reproducibility was defined by a coefficient of variation, calculated as the standard deviation of the FPG (or HbA1c) value at screening visit 1 and screening visit 2 divided by the corresponding mean value at these two visits for each participant.

2.3.2. Glycemic status at retesting

Among participants who met both FPG and HbA1c prediabetes criteria at screening visit 1, we calculated the proportions at screening visit 2 that retained the classification of prediabetes or were reclassified as having normal glucose regulation or diabetes. At screening visit 2, normal glucose regulation was defined as having all three results (FPG, HbA1c, 2hPG) in the normal range; prediabetes as having at least one result in the prediabetes range and none in the diabetes range; and diabetes as having at least one result above the diabetes cut point.

2.3.3. Development of the predictive model for diabetes at retesting

Because reclassification to diabetes would be clinically important, we developed a predictive model for detecting diabetes (i.e., at least one result above the diabetes cut point) at retesting given available data at screening visit 1. We chose an approach that would reduce model overfitting that consists of dividing the original cohort into training and test sets, and then further using tenfold cross-validation in the training set for model development. From the available cohort (N = 1271) we randomly selected two thirds as the training set and one third as the test set. In the training set, we used tenfold cross-validation to build and assess the performance of a predictive model for reclassification to diabetes at screening visit 2. We thus built a total of ten models, corresponding to each fold, and performed model estimation in each training partition and model assessment in each test partition. Tenfold cross validation reduces overfitting because model assessment is done on data not used for model fitting. We used logistic regression with linear predictors of FPG and HbA1c values at screening visit 1 to predict detection of diabetes at screening visit 2. We considered the following covariates to include in the model: age, sex, ethnicity, race, body mass index, family history of diabetes, use of antihypertensive or cholesterol medication, serum calcium, serum creatinine, and eGFR; however, unlike previous reports of prediction of impaired glucose tolerance [6], none of these variables were found to be statistically significant in univariate analysis; therefore,

they were not included in the predictive model to reduce the chance of overfitting and to preserve model simplicity and parsimony. We chose to include FPG and HbA1c as linear rather than categorical predictors as the linearity assumption was found to hold for each, and the resulting full model fit the data well with a smaller number of parameters. Discrimination was initially assessed in the training sample using area-under-the-curve or C-statistic (note the tenfold cross-validation resulted in exactly one predicted value for each sample). In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (LR+ and LR-) were assessed at a variety of thresholds of predicted diabetes detection. Calibration was assessed by generating a calibration curve at deciles of predicted detection and a Hosmer–Lemeshow statistic and p-value was calculated to assess model fit (Supplemental Fig. 2). Then, the model parameters were adjusted by fitting the model to the full training set and this model was applied to the test set and the previously-described tests and measures of discrimination and calibration were repeated. The use of a held-out test set is to verify that iterative model selection steps performed in the training set do not result in overfitting since the held-out test set is only tested once. The final model was generated by using the full cohort (training and test sets) to fit the model parameters. Discrimination and calibration as assessed in the training set within the tenfold cross-validation framework are presented as they have more precision, although the test set results are similar. All analyses were performed in R version 3.4.2 using functions from the PredictABEL and stats packages. The resultant predictive model allows the clinician to insert FPG and HbA1c values (within the prediabetes range) to calculate the probability that a participant would meet at least one criterion for diabetes upon retesting with FPG, HbA1c, and 2hPG.

3. Results

3.1. Participant characteristics

Baseline characteristics of the analytical cohort at screening visit 1 are shown in Table 1. The mean FPG was 109.4 mg/dL and the mean HbA1c was 5.9% (41 mmol/mol). The characteristics, which do not differ from the D2d trial cohort [7], approximate the ethnic and racial composition of the US population with the exception of a slightly lower representation of Hispanic participants [2,8].

Table 1
Demographics and clinical characteristics of participants at screening visit 1.

	n = 1271
Age, years	60.7 (9.5)
Age range, years, no. (%)	
25-44	72 (5.7)
45-59	445 (35.0)
≥60	754 (59.3)
BMI, kg/m^2	31.9 (4.5)
Self-reported family history of diabetes, no. (%)	764 (60.1)
Race, no. (%)	
Asian American	77 (6.1)
Black or African American	199 (15.7)
White	966 (76.0)
Other	29 (2.3)
Hispanic or Latino Ethnicity, no. (%)	99 (7.8)
HbA1c, mmol/mol	41.4 (2.1)
HbA1c, %	5.94 (0.19)
Fasting Plasma Glucose, mg/dL	109.4 (6.6)

Values are mean (SD) unless indicated otherwise. Race and ethnicity were reported by the patient. Racial and ethnic categories follow NIH guidelines. The category "other" includes American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; or Other race. Ethnicity includes any race.
Abbreviations: BMI, body mass index, NIH, National Institutes of Health; no., number; SD, standard deviation.

3.2. Reproducibility of glycemic measures

Fasting plasma glucose exhibited more variability than HbA1c between screening visit 1 and screening visit 2. Using data from the screening visit 1 and screening visit 2, the average coefficient of variation for FPG was 4.2% and the average coefficient of variation for HbA1c was 1.2%. Fig. 1(A and B) depicts the relationships between FPG and HbA1c values obtained at each of the two screening visits. 20.4% of FPG values and 9.1% of HbA1c values were outside of the prediabetes range at screening visit 2. Specifically, at screening visit 2, 16.5% of participants had normal FPG, and 3.9% had FPG in the diabetes range; 7.4% of participants had normal HbA1c and 1.7% of participants had an HbA1c in the diabetes range. Given both FPG and HbA1c in the prediabetes range at screening visit 1, only 1.6% of the time were both in the normal range at screening visit 2 (Table 2; 1.4% of the time FPG, HbA1c and 2hPG were in the normal range; 0.2% of the time FPG and HbA1c were in the normal range but 2hPG was in the prediabetes range).

3.3. Glycemic classification at retesting

Among participants with both FPG and HbA1c in the prediabetes range at screening visit 1, 98.6% had dysglycemia (i.e., a result in the prediabetes or diabetes range) when re-tested with FPG, HbA1c, and 2hPG a median of 21 days later (Table 2). At re-testing, 14.1% of participants could be categorized as diabetes based on having at least one glycemic value in the diabetes range. Among these participants, 62.6% met only the 2hPG criterion alone. Overall, 8.8% of the analyzed cohort could be categorized as diabetes by the 2hPG criterion alone. The frequency of participants reclassified as having normal glucose regulation or diabetes at screening visit 2, given varied combinations of FPG and HbA1c values at screening visit 1, is depicted in the surface plots in Fig. 2. Prediabetes classification was a continuum of risk for diabetes that rose as FPG and HbA1c values increased within the prediabetes range. For example, at screening visit 2, normal glucose regulation was present 2.1% of the time when FPG was 100 mg/dl and HbA1c was 5.7% (39 mmol/mol) at screening visit 1 (Fig. 2A). At screening visit 2, at least one test was in the diabetes range 70.3% of the time when FPG was 125 mg/dl and HbA1c was 6.4% (46 mmol/mol) at screening visit 1 (Fig. 2B).

3.4. Predictive model for diabetes at retesting

The parameters of the predictive model for detecting diabetes (defined as having at least one result above the diabetes cut point) at screening visit 2 in participants in whom both FPG and HbA1c values at screening visit 1 were in the prediabetes range are shown in Supplemental Table 1. In the training set, the model calibrated well (Supplemental Fig. 2) and showed good discrimination in the receiver operating characteristic curve with a C-statistic of 0.74 (Supplemental Fig. 3). The calibration and discrimination were also good in the test set with adequate calibration and a C-statistic of 0.81 (data not shown), indicating that overfitting did not occur and that the model generalizes well to participants whose data were not used in model development. Supplemental Table 2 shows the model characteristics of sensitivity, specificity, PPV, NPV, LR+ and LR-at designated thresholds of predicted risk of diabetes for the training set. For example, when the model predicted that the risk of diabetes at visit 2, given a certain combination of FPG and HbA1c at visit 1, was 0.3 (30%) or more, the positive predictive value at that threshold was 0.376

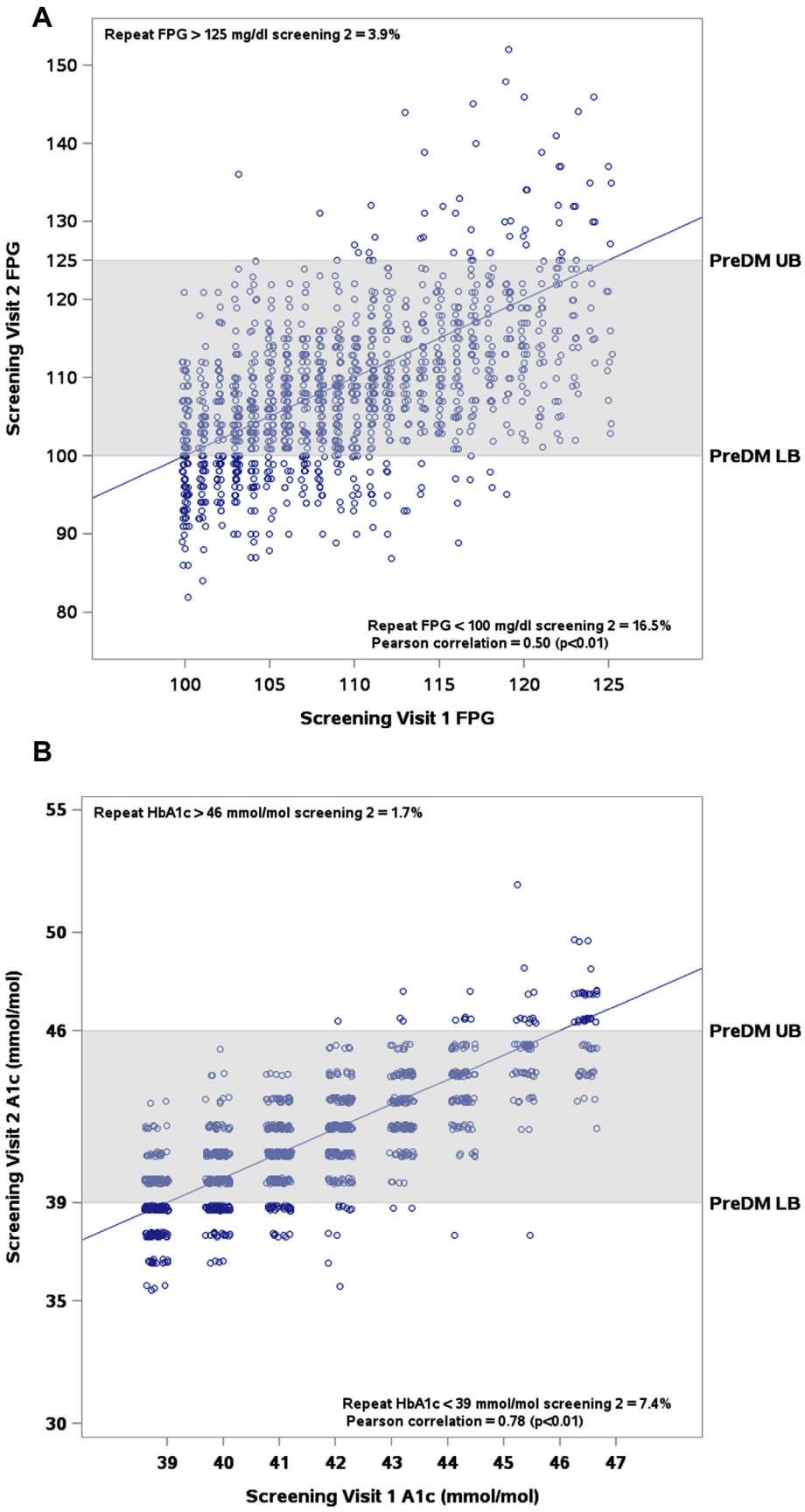

Fig. 1. (A)Values of fasting plasma glucose at screening visit 1 vs. screening visit 2. Shaded areas represent repeat values in the prediabetes range (FPG = 79.6%).
Abbreviations: FPG, fasting plasma glucose.
(B)Values of Hemoglobin A1c at screening visit 1 vs. screening visit 2. Shaded areas represent repeat values in the prediabetes range (HbA1c = 90.9%).

Table 2
Glycemic classification upon retesting (screening visit 2) among participants who met both FPG and HbA1c criteria for prediabetes at the screening visit 1.

Result at Screening Visit 2	No.	% of the cohort
All three glycemic tests in the normal range	**18**	**1.4**
Glycemic tests in prediabetes range	**1074**	**84.5**
HbA1c only	121	9.5
FPG only	44	3.5
2hPG only	2	0.2
HbA1c and FPG	455	35.8
HbA1c and 2hPG	59	4.6
FPG and 2hPG	25	2.0
FPG and HbA1c and 2hPG	368	29.0
Glycemic tests in diabetes range	**179**	**14.1**
HbA1c only	14	1.1
FPG only	21	1.7
2hPG only	112	8.8
HbA1c and FPG	1	0.1
HbA1c and 2hPG	3	0.2
FPG and 2hPG	24	1.9
FPG and HbA1c and 2hPG	4	0.3
Totals	**1271**	**100.0**

Ranges for normal, prediabetes and diabetes are defined by the 2010 American Diabetes Association criteria [4].

(namely, a 37.6% probability that the participant would have diabetes at visit 2) and a negative predictive value of 0.879 (namely, an 87.9% probability that a participant would not have diabetes on retest at visit 2) if the predicted risk was below 0.3.

4. Discussion

Our results show that when the two most commonly used glycemic tests in clinical practice (FPG and HbA1c) are both in the prediabetes range according to the current ADA criteria, it is nearly certain that re-testing which includes an OGTT will confirm dysglycemia (prediabetes or diabetes), obviating the need for an OGTT in most patients. To inform clinicians on the value of re-testing that includes an OGTT, we developed a simple prediction tool based on FPG and HbA1c values to estimate the likelihood of undetected diabetes in participants who have both FPG and HbA1c in the prediabetes range.

Several studies have documented limited sensitivity of measuring FPG or HbA1c alone as a screening tool for detecting prediabetes or diabetes [9–11]. As has been shown for predicting incident diabetes [12], our results indicate that measuring both FPG and HbA1c simultaneously to screen for prediabetes in a population at high risk for diabetes provides more meaningful information than either test alone. If results of both tests are within the prediabetes range, there is a high likelihood of participants having dysglycemia (prediabetes or diabetes) on re-testing, with a 98.6% positive predictive value. With this approach, 8.8% of our high-risk population had diabetes detected by the 2hPG criterion alone and 14.1% had diabetes detected by any of the glycemic criteria when retested on a different day. This prevalence is almost the same as found in the NHANES general (unselected) population in which 14.2% would be categorized as having diabetes by the 2hPG criterion among those meeting both FPG and HbA1c criteria for prediabetes when all criteria were assessed on the same day. Our data show that screening for diabetes, using FPG, HbA1c, and 2hPG in combination, can be done in a two-step process that is more convenient in typical clinical circumstances. The magnitude of the FPG and the HbA1c at the initial screening can guide the need for an OGTT (to test 2hPG) in a second step.

Our results confirm that the prediabetes classification includes a continuum of risk for diabetes that rises as FPG and HbA1c values increase within the prediabetes range [10]. We found that among participants with glycemic values in the diabetes range at screening visit 2, about two-thirds of the time (63%), diabetes was detected by the 2hPG criterion alone. To help clinicians predict the likelihood that diabetes would be detected upon reassessment that includes an OGTT, our straightforward prediction tool includes FPG and HbA1c as the only prediction variables. The predicted value from the model is provided as a continuous number, and the threshold of predicted diabetes risk that triggers doing an OGTT should be determined by a shared decision process between clinicians and participants. The resultant model is very simple, which optimizes utility; however, the model should be applied only in participants who underwent FPG and HbA1c testing because they were at risk for prediabetes based on non-laboratory criteria, similar to eligibility criteria for this trial (e.g., overweight, family history).

4.1. Limitations

In the present analysis, we define diabetes at screening visit 2 based on at least one positive test (FPG, HbA1c, or 2hPG), which contrasts with the ADA recommendation that requires confirmation of a single positive test. However, because the data relating glycemic tests to diabetes complications used to define the ADA diabetes diagnostic criteria likewise used a single measurement of FPG, HbA1c, and 2hPG, allowing a single test result to define diabetes does not diminish the significance of our findings [13–15]. The diagnostic approach we describe is meant to reflect the sequence of testing expected to occur in clinical practice; namely, assessment of FPG and HbA1c (given simplicity and low burden) followed by an OGTT if needed. In this usual sequence, it would be exceedingly unlikely for a second OGTT to be done to confirm a positive 2hPG. Another potential limitation is that the cohort size is relatively small for predictive model building; therefore, the model should be validated in a larger independent cohort. Finally, we were unable to assess the frequency of newly detected diabetes when only one of the screening tests was positive for prediabetes, because the parent study design called for both FPG and HbA1c to be in the prediabetes range to proceed to screening visit 2.

4.2. Strengths

The D2d study employed the FPG and HbA1c tests, which are commonly used in clinical practice for the initial identification of people with prediabetes. Individually, the FPG and HbA1c tests have limitations but using both tests in combination adds value to defining one's glycemic status. The D2d study eligibility criteria (e.g., overweight or obese, age > 30 years) are consistent with the high-risk factors that should be considered when screening for prediabetes. Therefore, results and the predictive model can be generalized to clinical practice. All tests at both visits were analyzed by the same laboratory, which precludes the need for statistical recalibration to ensure equivalence of measures over time as typically done in observational studies.

In conclusion, among people at risk for prediabetes/diabetes, the combination of both FPG and HbA1c in the prediabetes range indicated with near certainty the presence of dysglycemia (defined as a test result in the prediabetes or diabetes range) upon re-testing that included an OGTT. Further, the likelihood of having a positive test in the diabetes range upon re-testing followed a continuum of risk without a threshold effect. To better inform risk assessment and optimize re-testing with an OGTT, we have developed a simple predictive model that includes the simultaneously measured FPG and HbA1c values to estimate the likelihood of newly detected diabetes upon re-testing.

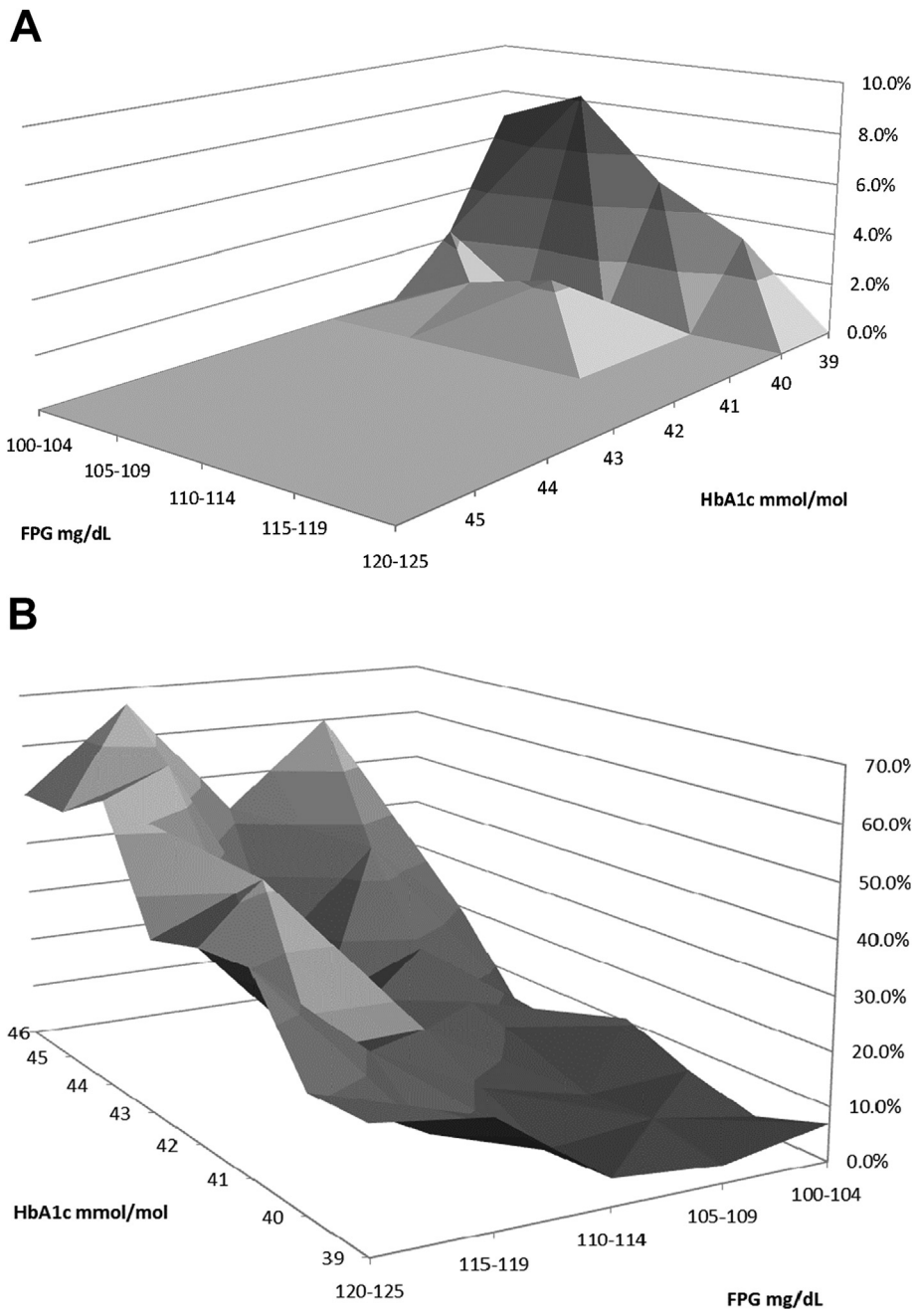

Fig. 2. (A)Surface Plot for proportion of participants meeting glycemic criteria for normal glucose regulation. Surface Plot for proportion of participants meeting glycemic criteria for normal glucose regulation at visit 2 (Z axis) given fasting glucose and HbA1c at screening visit 1 (X and Y axes).
(B)Surface Plot for proportion of participants meeting glycemic criteria for diabetes. Surface Plot for proportion of participants meeting glycemic criteria for diabetes at visit 2 (Z axis) given fasting glucose and HbA1c at screening visit 1 (X and Y axes).

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Authors' contributions

IB and CC designed the study; JN and CWL analyzed data; CC, IB, AGP, and CWL wrote manuscript draft; all authors contributed to the writing and critical review of the manuscript and approved the final version for publication. CWL, JN, and AGP are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Chhavi Chadha: Conceptualization, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Anastassios G. Pittas:** Supervision, Writing - original draft, Writing - review & editing. **Christine W. Lary:** Formal analysis, Writing - original draft, Writing - review & editing. **William C. Knowler:** Writing - review & editing. **Ranee Chatterjee:** Writing - review & editing. **Lawrence S. Phillips:** Writing - review & editing. **Vanita R. Aroda:** Writing - review & editing. **Michael R. Lewis:** Writing - review & editing. **Richard Pratley:** Writing - review & editing. **Myrlene A. Staten:** Writing - review & editing. **Jason Nelson:** Formal analysis, Writing - review & editing. **Neda Rasouli:** Writing - review & editing. **Irwin Brodsky:** Conceptualization, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2020.100031.

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