Identification of Persons at High Risk for Type 2 Diabetes Mellitus: Do We Need the Oral Glucose Tolerance Test?

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Background: The standard method of identifying persons at high risk for type 2 diabetes mellitus involves detection of impaired glucose tolerance, which requires a costly and inconvenient 2-hour oral glucose tolerance test. Because clinical trials have indicated that diabetes is preventable by using behavioral or pharmacologic interventions, less expensive methods of identifying high-risk persons are needed.

Objective: To determine whether multivariable models are superior to glucose tolerance tests for identifying persons at high risk for diabetes mellitus.

Design: Prospective cohort study.

Setting: San Antonio, Texas.

Participants: 1791 Mexican Americans and 1112 non-Hispanic whites without diabetes at baseline who were randomly selected from census tracts.

Measurements: Medical history; body mass index; blood pressure; fasting and 2-hour plasma glucose levels; fasting serum total, low-density lipoprotein, and high-density lipoprotein cholesterol levels; and triglyceride level.

Results: For prediction of 7.5-year incidence of type 2 diabetes, the area under the receiver-operating characteristic (ROC) curve for a multivariable model involving readily available clinical variables was significantly ($P < 0.001$) greater than the area under the ROC curve for the 2-hour glucose value alone (84.3% vs. 77.5%). Impaired glucose tolerance represents a single point on the latter curve. Adding the 2-hour glucose measurement to the multivariable model increased the area under its ROC curve, but only from 84.3% to 85.7%.

Conclusion: Persons at high risk for diabetes mellitus are better identified by using a simple prediction model than by relying exclusively on the results of a 2-hour oral glucose tolerance test. Although adding the 2-hour glucose variable to the model enhanced prediction, the resulting slight improvement entails greater cost and inconvenience.

In 1979, the National Diabetes Data Group defined an entity called impaired glucose tolerance, which reflects a degree of glucose tolerance that, although abnormal, is considered insufficient to merit a diagnosis of diabetes mellitus (1). This entity, which was later endorsed by the World Health Organization (WHO) (2, 3) and the American Diabetes Association (4), requires a 2-hour oral glucose tolerance test for its detection. It is important to emphasize that impaired glucose tolerance is by itself entirely asymptomatic and unassociated with any functional disability. Indeed, insulin secretion is typically greater in response to a mixed meal than in response to a pure glucose load (5); as a result, most persons with impaired glucose tolerance are rarely, if ever, hyperglycemic in their daily lives (5, 6), except when they undergo diagnostic glucose tolerance tests. Thus, the importance of impaired glucose tolerance resides exclusively in its ability to identify persons at increased risk for future disease.

The standard method for identifying persons at high risk for developing diabetes mellitus has been to identify persons with impaired glucose tolerance with-out regard to other diabetes risk factors. For example, nearly all of the clinical trials on prevention of type 2 diabetes have used impaired glucose tolerance as the principal enrollment criterion. Three of these trials—the Finnish Diabetes Prevention Study (7), the Diabetes Prevention Program (8), and the Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) (9)—have recently reported positive results. Therefore, a need has arisen to identify persons at high risk for diabetes so that physicians can offer them preventive interventions. Because the 2-hour oral glucose tolerance test, which is necessary for the diagnosis of impaired glucose tolerance, is time consuming, costly, and inconvenient, it becomes relevant to ask whether other, more efficient means exist for identifying persons at high risk for diabetes.

A popular method of assessing the predictive discrimination of a test is to use a receiver-operating characteristic (ROC) curve (10) that plots the sensitivity of the test against the corresponding false-positive rate. In the present context, *sensitivity* refers to the percentage of persons whose initial values were above a given cut point

Context

Lifestyle and pharmaceutical interventions can prevent overt diabetes in people with impaired glucose tolerance.

Oral glucose tolerance testing is the reference standard for identifying impaired glucose tolerance, but it is inconvenient and relatively expensive.

Contribution

The authors developed multivariable models that use readily available clinical variables to predict the development of diabetes.

The models were more accurate than oral glucose tolerance testing alone.

Adding results of oral glucose tolerance testing did not substantially improve the model's predictions.

Cautions

More than half the study sample was Mexican American.

Validation in other populations and translation for bedside calculation is needed before clinicians can use the model.

–The Editors

among all persons who later developed diabetes; *false-positive rate* refers to the percentage of persons whose initial values were above the cut point among persons who nevertheless remained free of diabetes. The area under the ROC curve is a measure of how well a continuous variable can predict the outcome of interest: If the sensitivity increases steeply as the threshold for diagnosis is relaxed, with only a relatively slow accumulation of false-positive results, the area under the ROC curve will be large; conversely, if the sensitivity increases slowly as the threshold for diagnosis is relaxed, with a rapid accumulation of false-positive results, the area under the ROC curve will be correspondingly smaller. The differences in the areas under two curves may be tested to see whether the apparent superiority of one continuous variable over another is statistically significant. We have used this approach to compare the 2-hour glucose value after an oral glucose load to various multivariable models for predicting future diabetes.

METHODS

Participants

Our analyses are based on data gathered in the San Antonio Heart Study. The methods of this study have been described elsewhere (11–13). Briefly, households were randomly sampled from three types of neighborhoods: low, middle, and high income. Residents of these households were eligible if they were 25 to 64 years of age and not pregnant. Because the number of non–Mexican-American persons residing in the low-income areas was negligible, only Mexican Americans were recruited from these neighborhoods. Stratified random sampling was used to recruit an approximately equal number of Mexican Americans and non-Hispanic whites from the middle-income and high-income neighborhoods.

The baseline data were collected in two phases, from 1979 to 1982 and from 1984 to 1988. A total of 5158 participants were enrolled in these two phases, representing a response rate of 65.3% of all eligible participants from the selected households. A follow-up examination was performed 7 to 8 years after the baseline examination on 3682 persons, representing 73.7% of the 4998 surviving study participants. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the protocol. All participants gave informed consent.

Measurements

Fasting plasma glucose levels were measured for all participants; they then drank a standardized 75-g glucose load (Koladex or Orangedex, Custom Laboratories, Baltimore, Maryland). The plasma glucose level was measured again 2 hours later. Although various protocols have been used for oral glucose tolerance testing, the glucose level obtained 2 hours after the administration of the oral glucose load is the only postload value that has been used as the basis for diagnostic categories (1–4); therefore, this was the only postload value that we considered. In line with common usage, we refer to this value as the 2-hour glucose value. Diabetes was diagnosed according to WHO criteria (fasting glucose level ≥ 7.0 mmol/L [≥ 126 mg/dL] or 2-hour glucose level ≥ 11.1 mmol/L [≥ 200 mg/dL]) (3). Persons who reported a history of diabetes diagnosed by a physician and who reported current use of insulin or an oral antidiabetic agent were considered to have diabetes regardless of their plasma glucose levels. Participants were asked to bring to the examination center a list of all prescription medications that they were receiving or the containers in which the medications had been dis-

pensed. Participants who did not adhere to this request were subsequently contacted by telephone to verify their medications. Participants were classified as having diabetes if they met at least one of the above three criteria (fasting glucose value, 2-hour glucose value, or antidiabetic medications), even if all three variables were not recorded. Participants were classified as nondiabetic if all three variables were recorded and none met the criterion for diabetes. Persons with diabetes who were not taking insulin were considered to have type 2 diabetes. Participants with diabetes who used insulin were considered to have type 2 diabetes if they were at least 30 years of age at diabetes onset and if their body mass index (BMI) (weight in kg divided by height in meters squared) was greater than 27.0 kg/m^2. Nondiabetic persons were classified as having impaired glucose tolerance if their 2-hour plasma glucose level was 7.8 mmol/L or higher (≥140 mg/dL) but less than 11.1 mmol/L (<200 mg/dL) (1–4). Height; weight; blood pressure; plasma glucose level; serum total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels; and serum triglyceride level were measured by using previously reported methods (11, 12).

Statistical Analysis

Baseline characteristics of the study sample according to sex and ethnicity were adjusted for age by analysis of covariance using SAS software (14). We developed a multiple logistic regression model with incident diabetes as the dependent variable and a panel of baseline characteristics that are ordinarily available in a routine clinical setting as independent variables. We refer to this model—which includes (with or without selected interactions, as explained in the Results section) age; sex; ethnicity; fasting and 2-hour glucose levels; systolic and diastolic blood pressures; total, LDL, and HDL cholesterol levels; triglyceride level; body mass index; and parental or sibling history of diabetes—as the *full model*. In addition to testing the statistical significance of each interaction term, we also used likelihood ratio tests to globally compare models with and without interactions. We assessed the importance of the 2-hour glucose value for predicting diabetes by comparing the full model with a nested model that excluded the 2-hour glucose value.

We also examined a simplified model based on widely recognized diabetes risk factors, which we call the *clinical model*. We believe that clinicians would more readily accept this simplified model because it entails fewer variables. The variables used in the clinical model were age, sex, ethnicity, fasting glucose level, systolic blood pressure, HDL cholesterol level, body mass index, and parental or sibling history of diabetes. This model was also examined with and without selected interactions and with and without 2-hour glucose value. We assessed the goodness of fit of all models by using the Hosmer–Lemeshow test (14).

We compared the predictive discrimination of the multivariable models to the predictive discrimination of the 2-hour glucose measurement by using ROC curves. The cutoff point defining impaired glucose tolerance represents only one of many possible cutoff points along the 2-hour glucose curve. The ROC curves were calculated for the multivariable models and for 2-hour glucose concentration by using SAS PROC LOGISTIC software (14), and were plotted for each 1% increment of the false-positive rate. The diabetes risks predicted for each person by the multivariable models were used in the analysis of the ROC curve. We used Stata software (15) to estimate the 95% CIs of the areas under the ROC curves and the statistical significance of differences between these areas according to the algorithm developed by DeLong and colleagues (16). We also compared nested models by using likelihood ratio testing. The 95% CIs of the areas under the ROC curves and the statistical significance of differences in the areas were then validated by use of the internal bootstrap resampling procedure (1000 samples with replacement) described by Harrell (17).

Role of the Funding Source

RESULTS

Of the 1838 Mexican Americans and 1166 non-Hispanic white persons without diabetes at the baseline examination, 208 Mexican Americans and 67 non-Hispanic whites developed type 2 diabetes in the 7.5-year follow-up period. Excluded from these tallies are 354 persons with diabetes at baseline, 192 whose diabetes status was indeterminate at baseline, and 132 whose di-

Table 1. Age-Adjusted Diabetes Risk Factors at Baseline, according to Ethnicity and Sex, in the San Antonio Heart Study*

Variable	Mexican Americans		Non-Hispanic White Persons	
	Men (n = 732)	Women (n = 1059)	Men (n = 492)	Women (n = 620)
Age, y‡	42.6 ± 0.40	42.8 ± 0.33	44.6 ± 0.48	44.8 ± 0.43
Fasting blood glucose level, mmol/L (mg/dL)	5.0 ± 0.02 (90.1 ± 0.36)	4.8 ± 0.02 (87.2 ± 0.30)	5.0 ± 0.02 (89.6 ± 0.44)	4.8 ± 0.02 (86.2 ± 0.39)
2-Hour glucose level, mmol/L (mg/dL)	5.9 ± 0.06 (106.4 ± 1.11)	6.3 ± 0.05 (113.6 ± 0.92)	5.5 ± 0.08 (99.2 ± 1.35)	5.7 ± 0.07 (102.3 ± 1.21)
Systolic blood pressure, mm Hg	120.1 ± 0.49	113.1 ± 0.41	117.0 ± 0.60	110.0 ± 0.54
Diastolic blood pressure, mm Hg	74.8 ± 0.33	70.3 ± 0.27	73.0 ± 0.40	68.3 ± 0.35
Total cholesterol level, mmol/L (mg/dL)	5.4 ± 0.04 (208.0 ± 1.38)	5.1 ± 0.03 (198.6 ± 1.15)	5.2 ± 0.04 (202.2 ± 1.69)	5.2 ± 0.04 (201.2 ± 1.50)
LDL cholesterol level, mmol/L (mg/dL)	3.4 ± 0.03 (130.4 ± 1.26)	3.1 ± 0.03 (119.7 ± 1.05)	3.3 ± 0.04 (126.5 ± 1.54)	3.1 ± 0.04 (119.3 ± 1.37)
HDL cholesterol level, mmol/L (mg/dL)	1.2 ± 0.01 (46.2 ± 0.53)	1.4 ± 0.01 (54.3 ± 0.44)	1.3 ± 0.02 (48.6 ± 0.65)	1.6 ± 0.01 (60.6 ± 0.58)
Triglyceride level, mmol/L (mg/dL)	1.9 ± 0.04 (171.7 ± 3.28)	1.4 ± 0.03 (126.4 ± 2.73)	1.6 ± 0.05 (143.1 ± 4.00)	1.2 ± 0.04 (108.1 ± 3.57)
Body mass index, kg/m²	28.1 ± 0.19	27.9 ± 0.16	26.5 ± 0.23	24.8 ± 0.20
Family history of diabetes, %§	39.6	33.7	21.0	15.6

* Values with the plus/minus sign are the mean ± SE. HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† P values are for the main effects of ethnicity, sex, and the interaction between ethnicity and sex.
‡ Unadjusted variable.
§ Participants were considered to have a family history if they had a parent or sibling with diabetes mellitus. This variable was adjusted for age by using logistic regression.

abetes status was indeterminate at follow-up. (Participants with indeterminate status had no evidence of diabetes but were missing values for at least one of the three study criteria for diabetes classification.) Of the 275 participants with incident diabetes, 221 were not receiving pharmacologic treatment for diabetes and were given a diagnosis exclusively on the basis of plasma glucose levels that met the WHO criteria (3). Of the 54 participants with confirmed pharmacologic treatment for diabetes, 45 also met one or both plasma glucose criteria for diabetes. Thus, only 9 incident cases of diabetes were diagnosed exclusively on the basis of medication history. The analyses presented here also exclude data on 101 persons with missing values for at least one predictor variable. Thus, our analyses are based on the data of 1791 Mexican Americans and 1112 non-Hispanic whites, of whom 204 Mexican Americans and 65 non-Hispanic whites developed diabetes.

Table 1 shows age-adjusted baseline characteristics of the study sample according to sex and ethnicity. We observed significant sex-by-ethnicity interactions for total and HDL cholesterol levels and for body mass index. The logistic regression coefficients, however, were not statistically significant for any of these interactions in the full or clinical model, and the global likelihood ratio test of these models with and without the interaction terms was likewise not significant. Therefore, we did not further consider models with interactions.

Table 2 shows the areas under the ROC curves,

their 95% CIs, their Hosmer–Lemeshow goodness-of-fit statistics, and tests of the statistical significance of the differences between various models by using the DeLong algorithm (16) and, for comparison of nested models, likelihood ratio tests. The Hosmer–Lemeshow test did not reject the goodness of fit for any of the models.

The principal finding presented in Table 2 is that all of the multivariable models outperformed the model that relies exclusively on the 2-hour glucose measurement in predicting future type 2 diabetes—that is, the areas under their ROC curves are in every case larger than the areas under the ROC curves for 2-hour glucose measurement alone. The multivariable model with the smallest area under its ROC curve—namely, the clinical model *without* 2-hour glucose—significantly outperformed the model consisting exclusively of the 2-hour glucose value; moreover, the other multivariable models performed at least as well as the model consisting of 2-hour glucose value alone. The full model with or without 2-hour glucose measurement was not significantly better than the corresponding clinical models. For both the full model and the clinical model, inclusion of the 2-hour glucose value significantly increased the areas under the ROC curves, but the improvements in both cases were less than 1.5%. (The 95% CIs obtained by the bootstrap procedure were similar to those shown in Table 2 [obtained by using the DeLong algorithm].) The significance of the differences between areas under

Table 1—Continued

P Values for Main Effects and Interactions†		
Ethnicity	**Sex**	**Ethnicity × Sex**
<0.001	>0.2	>0.2
0.0393	<0.001	>0.2
<0.001	<0.001	0.0776
<0.001	<0.001	>0.2
<0.001	<0.001	>0.2
>0.2	<0.001	0.0038
0.1586	<0.001	0.1749
<0.001	<0.001	<0.001
<0.001	<0.001	0.1312
<0.001	0.001	<0.001
<0.0056	<0.001	>0.2

the ROC curves shown in **Table 2** were also validated by the bootstrap procedure—that is, the 95% CIs of the differences in areas obtained by the bootstrap procedure excluded zero when the other tests were statistically significant and included zero when the other tests were not statistically significant. In particular, in 95% of replications the areas under the ROC curves for the models that included 2-hour glucose measurement exceeded the areas under the corresponding ROC curves that excluded 2-hour glucose value by not more than 2.8% and

not less than 0.5%. The parameter estimates for the clinical model with the 2-hour glucose value excluded are given in the Appendix. The parameter estimates for the other models are available from the authors upon request.

The **Figure** provides a visual representation of selected ROC curves and shows that both multivariable models are superior to the model based exclusively on 2-hour glucose value. The position of impaired glucose tolerance on the 2-hour glucose curve is indicated. The sensitivity and false-positive rate of impaired glucose tolerance are 50.9% and 10.2%, respectively. The **Figure** shows that at the same false-positive rate, the clinical model has slightly better sensitivity. However, this sensitivity and false-positive rate can be achieved by using the clinical model without performing an oral glucose tolerance test. If a higher sensitivity is desired, the clinical model is clearly superior to relying on the 2-hour glucose value alone.

DISCUSSION

Overwhelmingly, the method used for identifying persons at high risk for diabetes in research applications has been to select persons with impaired glucose toler-

Table 2. **Areas under Receiver-Operating Characteristic Curves for Models Predicting the 7.5-Year Incidence of Type 2 Diabetes Mellitus in the San Antonio Heart Study***

Models and Model Comparisons	Area Under the Receiver-Operating Characteristic Curve (95% CI), %	P Value (Hosmer–Lemeshow)†	P Values for Model Comparisons	
			DeLong‡	**Likelihood Ratio Test§**
Models				
Full model with 2-h glucose	85.9 (83.6–88.3)	>0.2		
Full model—no 2-h glucose	84.5 (82.0–87.0)	0.12		
Clinical model with 2-h glucose	85.7 (83.4–88.2)	>0.2		
Clinical model—no 2-h glucose	84.3 (81.8–86.7)	>0.2		
2-Hour glucose	77.5 (74.3–80.7)	0.20		
Comparisons between models				
Full model with 2-h glucose vs. full model—no 2-h glucose			0.020	<0.001
Full model with 2-h glucose vs. clinical model with 2-h glucose			0.105	>0.2
Full model—no 2-h glucose vs. clinical model—no 2-h glucose			0.079	0.18
Clinical model with 2-h glucose vs. clinical model—no 2-h glucose			0.015	<0.001
Clinical model—no 2-h glucose vs. 2-h glucose			<0.001	—‖

* The models assessed were full or clinical multivariable models with or without 2-hour plasma glucose value and 2-hour plasma glucose level only. The clinical multivariable models used the following variables: age, sex, ethnicity, fasting glucose level, systolic blood pressure, high-density lipoprotein cholesterol level, body mass index, and parent or sibling with diabetes. The full multivariable models included all variables from the clinical model plus diastolic blood pressure, total and low-density lipoprotein cholesterol levels, and triglyceride level.
† P values calculated by using the Hosmer–Lemeshow goodness-of-fit test.
‡ P values for test of difference in areas under two receiver-operating characteristic curves; calculated by using the method developed by DeLong and colleagues (16).
§ P value for the likelihood ratio test.
‖ Not applicable for nonnested models.

Figure. **Receiver-operating characteristic curves for the full multivariable model with 2-hour glucose value included, the clinical model with the 2-hour glucose measurement excluded, and the 2-hour glucose variable by itself.**
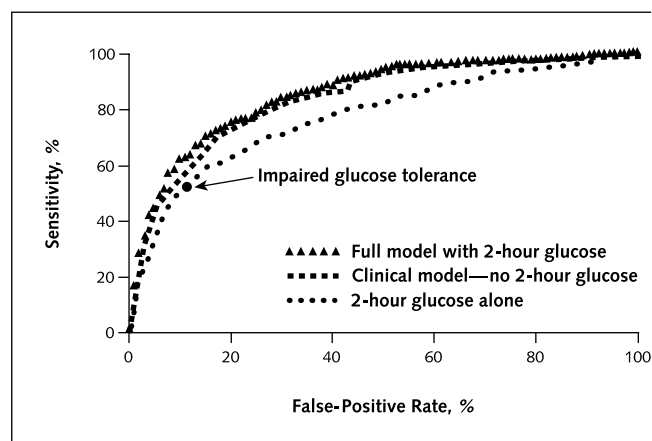
The location (*large circle*) of impaired glucose tolerance (plasma glucose level ≥7.8 mm/L [≥140 mg/dL]) on the 2-hour glucose curve is indicated.

ance with minimal or no regard to other diabetes risk factors (7–9). Impaired glucose tolerance is defined by the plasma glucose level measured 2 hours after an oral glucose load; thus, a 2-hour glucose tolerance test is necessary to identify persons in this category. Because of its cost and inconvenience, the oral glucose tolerance test has been met with considerable resistance and is rarely used in ordinary clinical practice (4, 18). Because clinical trials have documented that diabetes can be prevented by behavioral or pharmacologic interventions (7–9), there is a need to develop methods to identify persons at high risk for diabetes by using techniques that will be widely accepted in clinical and public health settings, not just in research settings. Our results suggest that using a simple multivariable model—consisting of readily available clinical measurements, most of which are routinely gathered anyway, and not requiring a 2-hour oral glucose tolerance test—is superior to relying exclusively on the 2-hour glucose value for identifying persons at high risk for future type 2 diabetes. We believe that this simple clinical model will be more readily accepted by clinicians because it contains fewer variables and is not significantly inferior to the full model in predictive discrimination. Although the addition of the 2-hour glucose value to either multivariable model im-

proved its predictive discrimination even further, the improvements were minor relative to the differences in predictive discrimination between the multivariable models and exclusive reliance on 2-hour glucose value. Moreover, addition of the 2-hour glucose value to the multivariable models would probably undermine patients' and clinicians' acceptance of this method (4, 18).

Although the 2-hour glucose value may add little to identifying persons at risk for future diabetes, oral glucose tolerance tests are arguably still needed to diagnose prevalent cases of diabetes in which the only manifestation of the disease is an abnormal 2-hour glucose value. Although the American Diabetes Association has taken the position that identifying such cases is not mandatory (4), the WHO has dissented from this viewpoint (3). A full discussion of this matter is beyond the scope of the present paper; however, it should be noted that no clinical trial has ever focused specifically on the benefits of treating such patients instead of waiting until they manifest fasting hyperglycemia. Moreover, patients whose diabetes is diagnosed solely on the basis of an abnormal 2-hour value have a high rate of reversion to normal on follow-up and may in fact represent false-positive diagnoses. We have previously reported, for example, that such cases were almost 5 times more likely to revert to nondiabetic status after 7 to 8 years of follow-up compared with persons meeting conventional fasting or clinical diagnostic criteria (19).

In addition to inconvenience, cost is another obstacle to the widespread adoption of the 2-hour oral glucose tolerance test as a screening tool for identifying persons with impaired glucose tolerance. The American Diabetes Association has recommended screening criteria for diabetes (4). The clinical model, the details of which are given in the Appendix, could be incorporated as it stands into clinical practice and public health practice with the aid of a hand-held, programmable calculator or a personal computer. The model could be used in clinical practice to support patient counseling and in public health practice to identify target populations for preventive interventions. Before such a clinical and public health tool is adopted, however, certain limitations of the present study need to be acknowledged. First, the estimates of the model parameters could be biased by the persons whose diabetic status was unknown because of missing data at baseline or follow-up or because they died before follow-up. This limitation indicates a need

to validate the model in other populations. In addition to further validation in populations similar to those in our analysis, the model should be validated in other high-risk ethnic groups, such as Native Americans and African Americans, as well as non-U.S. populations. Clearly, we cannot state with confidence that our model would perform satisfactorily in these ethnic groups because they were not included in the present study. Because the development of diabetes has been studied in many prospective cohort studies, most of which have contained all, or at least most, of the risk factors in our analysis, we hope that this report will stimulate other researchers with suitable databases to evaluate prediction models for type 2 diabetes similar to those presented here.

APPENDIX

The following are parameter estimates for the clinical model without the value for the glucose level obtained 2 hours after the administration of an oral glucose load:

$p = 1/(1 - e^{-x})$, where $x = -13.415 + 0.028(\text{age}) + 0.661(\text{sex}) + 0.412(\text{MA}) + 0.079(\text{FG}) + 0.018(\text{SBP}) - 0.039(\text{HDL}) + 0.070(\text{BMI}) + 0.481(\text{family history})$. In this equation, p = the probability of developing diabetes over the 7.5 year follow-up period; age is in years; sex = 1 if female, 0 if male; MA = 1 if Mexican American, 0 if non-Hispanic white; FG = fasting glucose in mg/dL; SBP = systolic blood pressure in mm Hg; HDL = high-density lipoprotein cholesterol level in mg/dL; BMI = body mass index in kg/m^2; and family history = 1 if at least one parent or sibling has diabetes or 0 if not.

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