Fasting Plasma Glucose and Hemoglobin A_{1c} in Identifying and Predicting Diabetes

The Strong Heart Study

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OBJECTIVE—To compare fasting plasma glucose (FPG) and HbA_{1c} in identifying and predicting type 2 diabetes in a population with high rates of diabetes.

RESEARCH DESIGN AND METHODS—Diabetes was defined as an FPG level ≥126 mg/dL or an HbA_{1c} level ≥6.5%. Data collected from the baseline and second exams (1989–1995) of the Strong Heart Study were used.

RESULTS—For cases of diabetes identified by FPG ≥126 mg/dL, using HbA_{1c} ≥6.5% at the initial and 4-year follow-up diabetes screenings (or in identifying incident cases in 4 years) among undiagnosed participants left 46% and 59% of cases of diabetes undetected, respectively, whereas for cases identified by HbA_{1c} ≥6.5%, using FPG ≥126 mg/dL left 11% and 59% unidentified, respectively. Age, waist circumference, urinary albumin-to-creatinine ratio, and baseline FPG and HbA_{1c} levels were common significant risk factors for incident diabetes defined by either FPG or HbA_{1c}; triglyceride levels were significant for diabetes defined by HbA_{1c} alone, and blood pressure and sibling history of diabetes were significant for diabetes defined by FPG alone. Using both the baseline FPG and HbA_{1c} in diabetes prediction identified more people at risk than using either measure alone.

CONCLUSIONS—Among undiagnosed participants, using HbA_{1c} alone in initial diabetes screening identifies fewer cases of diabetes than FPG, and using either FPG or HbA_{1c} alone cannot effectively identify diabetes in a 4-year periodic successive diabetes screening or incident cases of diabetes in 4 years. Using both criteria may identify more people at risk. The proposed models using the commonly available clinical measures can be applied to assessing the risk of incident diabetes using either criterion.

Diabetes Care 34:363–368, 2011

Type 2 diabetes has emerged as an important public health and economic problem in the U.S. More than 18 million Americans have diabetes and are at risk for related complications including heart disease, stroke, retinopathy, leg vessel disease, and kidney disease (1). Currently available therapeutic strategies in diabetes are only partially successful in preventing its complications. Therefore, diabetes screening in undiagnosed participants and early identification of those at high risk for intervention to prevent diabetes onset is very important for reducing diabetes-associated complications and medical care costs.

Criteria proposed for diagnosing incident diabetes by the American Diabetes Association (ADA) (2) based on fasting plasma glucose (FPG) have been used for a long time. Recently, an International Expert Committee (3) recommended a criterion based on HbA_{1c}. The cutoff point of an HbA_{1c} ≥6.5% suggested in their report was based on the association of HbA_{1c} with the prevalence of retinopathy from large cross-sectional studies (3). The ADA recently added HbA_{1c} as a diagnostic criterion of diabetes and suggested using either criterion (4). Therefore, it is important to know how these criteria perform in identifying prevalent diabetes in initial and successive diabetes screenings among undiagnosed participants and incident diabetic case subjects in a period of time and which risk factors predict incident diabetes defined by these criteria.

This report used longitudinal data from two exams (1989–1992 and 1993–1995) of the Strong Heart Study (SHS), a study to assess the prevalence and incidence of cardiovascular disease (CVD) and its risk factors in American Indians (5). This population has high rates of diabetes, and data from this population may be considered to be reflective of other populations who are at high risk for diabetes and diabetic CVD (6,7). This research compares the diagnosis of diabetes by HbA_{1c} or/and FPG and the risk factors for incident diabetes defined by the three criteria and develops prediction equations for incident diabetes using baseline HbA_{1c}, FPG, or both.

RESEARCH DESIGN AND METHODS

—A total of 4,549 American Indian men and women, aged 45–74 years, in 13 Indian tribes/communities in Arizona, North/South Dakota, and Oklahoma, participated in the SHS baseline examination from 1989 to 1992 after providing written informed consent. The study was approved by all participating Indian tribes/communities and the Institutional Review Boards of the participating institutions and the Indian Health Service. The cohort was followed and

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Received 30 August 2010 and accepted 21 November 2010.
DOI: 10.2337/dc10-1680
The views expressed in this article are those of the authors and do not necessarily reflect those of the Indian Health Service.

reexamined in 1993–1995. The design and methods of the SHS have been previously reported in detail (5). Briefly, each examination included a personal interview and a physical examination. Blood was drawn at each examination after a 12-h fast, and total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides (TGs), and FPG were measured. Diabetes status was defined by ADA 2004 criteria based on FPG (denoted as FPG-DM) (2) as diabetes if FPG ≥126 mg/dL or if on diabetes medications, as impaired fasting glucose (IFG) (or prediabetes) if 100 ≤ FPG < 126 mg/dL, and as normal fasting plasma glucose (NFG) if FPG <100 mg/dL; by International Expert Committee criteria based on HbA$_{1c}$ (denoted as A1C-DM) (3) as diabetes if HbA$_{1c}$ ≥6.5% or if on diabetes medications, prediabetes if 6.0 ≤ HbA$_{1c}$ < 6.5%, and nondiabetes otherwise; and by current ADA criteria based on both HbA$_{1c}$ and FPG (denoted as FPG/A1C-DM) (4) as diabetes if HbA$_{1c}$ ≥6.5% or FPG ≥126 mg/dL or if on diabetes medications and nondiabetes otherwise. A urine sample was taken to measure albumin and creatinine. Albuminuria was classified by urinary albumin-to-creatinine ratio (UACR) as microalbuminuria if 30 ≤ UACR < 300 mg/g and macroalbuminuria if UACR ≥300 mg/g. Obesity status was defined as obese if BMI ≥30 kg/m^2, overweight if 25 ≤ BMI < 30 kg/m^2, and normal if BMI <25 kg/m^2. Three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken on the right arm with an appropriately sized cuff using a Baum mercury sphygmomanometer (W.A. Baum Co., Copiague, NY) after the participant rested in a seated position for 5 min. The average of the second and third measurements was used as the blood pressure value for each participant. According to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) criteria (8), hypertension (HTN) was defined as SBP/DBP ≥140/90 mmHg or on antihypertensive medications, normal if SBP <120 mmHg and DBP <80 mmHg, and prehypertension (Pre-HTN) otherwise. Leisure-time activities were measured at the baseline exam by the average exercise hours in the past week (AEHPW).

Metabolic syndrome traits described by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria (9) were also used in classification. Participants with SBP/DBP ≥130/85 mmHg or on treatment for hypertension were considered as having elevated blood pressure; waist circumference (WAIST) >102 cm in men or >88 cm in women was considered high (highWAIST); fasting TG ≥150 mg/dL was considered hypertriglyceridemia (hyperTG); and HDL-C <40 mg/dL in men or <50 mg/dL in women was considered low (lowHDL-C).

Data collected at the baseline and second exams from those participants who had HbA$_{1c}$ and FPG measured and did not receive insulin treatment or an oral agent for diabetes, were not on renal dialysis, and did not have a kidney transplant were used to compare the performances of HbA$_{1c}$ and FPG in identifying diabetes in undiagnosed participants. The risk factors data from the baseline exam and the incident diabetes status data from the second exam collected from participants without FPG-DM, A1C-DM, or FPG/A1C-DM at the baseline exam were used to explore significant predictors for cumulative incident FPG-DM, A1C-DM, and FPG/A1C-DM, respectively, and to compare effects of the baseline HbA$_{1c}$ or/and FPG in predicting the incident FPG/A1C-DM.

Statistical analyses

Frequency tables were used to explore the performances of HbA$_{1c}$ and FPG in identifying diabetes in undiagnosed participants. Logistic regression models (10) were used to compare risks of cumulative incident diabetes among subgroups of each risk factor after adjusting for age, sex, and center and to identify risk factors and build predictive models for cumulative incident FPG-DM, A1C-DM, and FPG/A1C-DM. Model-developing procedures were as follows: Step 1, candidate variables/risk factors for incident diabetes were selected among all potential categorical and continuous variables in the SHS data by a stepwise selection method with $P = 0.05$ for both entry and retention. These variables/risk factors included those reported in the literature (11–13) (i.e., age, sex, height, BMI, WAIST, SBP, DBP, current smoking status, hypertension status, parental or sibling history of diabetes, FPG, TC, LDL-C, HDL-C, TG, and the categorical metabolic syndrome traits) and additional variables (AEHPW, years of education, current alcohol intake, HbA$_{1c}$, and UACR). Step 2, the final model was derived by adding those additional significant ones that were selected by the stepwise method again among the squares and interactions of those selected candidate continuous variables in the model selected at Step 1. Step 1 was for selecting an optimal subset of significant and independent risk factors of incident diabetes among all potential subsets of the candidate risk factors. Step 2 considered potential interaction and nonlinear relations of the selected candidate variables with incident diabetes. The ability of the predictive models to discriminate participants who will or will not develop diabetes was assessed by the area under the receiver operating characteristic curve (AROC) (14). An AROC value ≥0.70 indicates good discrimination ability. The performance of the proposed models was also assessed for calibration by comparing the number of observed and predicted diabetes events in 4 years using a Hosmer-Lemeshow statistic (15). A value of this statistic <20 is considered good calibration. The discrimination and calibration abilities of the derived predictive models were further internally validated by using internal bootstrap resampling (1,000 samples with the same size as the original cohort and with replacement) method described by Harrell et al. (16). The bootstrap-corrected AROC and *P* value of the Hosmer-Lemeshow statistic were used in assessing internal validation (16). To compare performances of two different predictive models, we compared their AROCs (17). Statistical significance was defined as two-tailed $P < 0.05$ for all tests unless otherwise specified. SAS 9.1 was used for all analyses.

RESULTS—The baseline characteristics from the SHS have been reported previously (6). Table 1 shows HbA$_{1c}$ by FPG classification based on data from the SHS participants who had HbA$_{1c}$ and FPG measured and did not receive diabetes medications, were not on renal dialysis, and did not have a kidney transplant at the baseline exam (n = 2,849) or at the second exam (n = 1,670 after excluding also all participants who had FPG/A1C-DM at the baseline exam). Therefore, the data from the baseline exam represent results of initial diabetes screening by using HbA$_{1c}$ or FPG in undiagnosed participants, whereas the data from the second exam, an average of 4 years after the initial screening, represent incident cases in participants without diabetes at baseline.

For prevalent cases of diabetes, based on the results from the baseline exam, HbA$_{1c}$ (≥6.5%) identified only 54%

Table 1—*HbA_{1c} by FPG classification based on data from the baseline and second exams (1989–1995) of the SHS collected from American Indian participants who did not receive treatments for diabetes, were not on renal dialysis, and did not have a kidney transplant at the exams*

	Baseline exam FPG (mg/dL) (*N* = 2,849)			Second exam FPG (mg/dL) (*N* = 1,670)*		
	≥126	100–125	<100	≥126	100–125	<100
HbA_{1c} (%)						
≥6.5						
Frequency	314	33	4	71	70	34
Row percentage	89.5	9.4	1.1	40.6	40.0	19.4
Column percentage	54.2	2.5	0.4	40.6	8.2	5.3
6.0–6.4						
Frequency	73	92	29	19	66	38
Row percentage	37.6	47.4	15.0	15.5	53.7	30.9
Column percentage	12.6	7.0	3.0	10.9	7.7	5.9
4.75–5.9						
Frequency	167	938	603	68	562	371
Row percentage	9.8	54.9	35.3	6.8	56.1	37.1
Column percentage	28.8	71.4	63.1	38.9	65.7	58.0
<4.75						
Frequency	25	251	320	17	157	197
Row percentage	4.2	42.1	53.7	4.6	42.3	53.1
Column percentage	4.3	19.1	33.5	9.7	18.4	30.8

*Those participants with FPG ≥126 mg/dL, HbA_{1c} ≥6.5%, or on diabetes medications at the baseline exam were excluded. Row percentage 89.5 = 100 × 314/(314 + 33 + 4). Column percentage 54.2 = 100 × 314/(314 + 73 + 167 + 25).

[314/(314 + 73 + 167 + 25)] of those identified by FPG (≥126 mg/dL), whereas FPG identified 89% [314/(314 + 33 + 4)] of those diagnosed by HbA_{1c} (Table 1). Using HbA_{1c} alone identified only 57% [(314 + 33 + 4)/(314 + 73 + 167 + 25 + 33 + 4)] of all prevalent FPG/A1C-DM cases, whereas using FPG alone identified 94% [(314 + 73 + 167 + 25)/616]. For identifying cases of incident diabetes in 4 years, based on the results from the second exam, either HbA_{1c} or FPG identified only 41% of those diagnosed by the other. Using either HbA_{1c} or FPG alone identified 63% (175/279) of all incident FPG/A1C-DM cases. Because the data from the second exam also represent results from a 4-year periodic successive diabetes screening in participants without diabetes at baseline, this is also implied that for identifying cases of prevalent diabetes in a 4-year periodic successive diabetes screening in undiagnosed participants, using either FPG or HbA_{1c} alone identified only 63% of all FPG/A1C-DM cases.

For cases of prevalent prediabetes in the baseline exam, among undiagnosed participants HbA_{1c} (6–6.4%) identified 7% of those diagnosed by FPG (100–125 mg/dL), whereas FPG (100–125 mg/dL) identified 47% of those diagnosed by HbA_{1c} (6–6.4%); in the second exam, HbA_{1c} identified 8% of those diagnosed by FPG, and FPG diagnosed 54% of those diagnosed by HbA_{1c}.

To examine how A1C-DM criterion from a single exam relate to the clinical requirement of a repeat value for diagnosis, we have evaluated those 277 undiagnosed baseline diabetic participants who had HbA_{1c} ≥6.5% at the baseline exam and who also participated in the second exam. A total of 246 (88.8%) of the 277 undiagnosed participants received diabetes treatments (182) before the second exam or still had HbA_{1c} ≥6.5% at the second exam; 258 (93.1%) of the 277 received diabetes treatments or had either HbA_{1c} ≥6.5% or FPG ≥126 mg/dL at the second exam.

Table 2 compares the risks of developing incident A1C-DM, or FPG-DM, or FPG/A1C-DM in 4 years among subgroups of each risk factor commonly available in clinical practice after adjusting for age, sex, and center. For example, participants with 6.0% ≤ HbA_{1c} < 6.5% at the baseline exam had 5.89 times higher risk of developing A1C-DM in 4 years than those with HbA_{1c} <6.0%; participants with IFG at the baseline exam had 3.12 times higher risk of developing FPG-DM in 4 years than those with NFG. The table also shows odds ratios among strata of each risk factor for incident FPG/A1C-DM. From these adjusted univariate analyses, in addition to baseline glycemia, hypertension, obesity, highWAIST, family history, micro/macro-albuminuria, hyperTG, and lowHDL-C were all significant risk factors for incident diabetes identified by either criterion.

Predictive models for cumulative incidence of diabetes in 4 years are shown in Table 3. Age, waist circumference, UACR, and baseline FPG and HbA_{1c} levels were common significant risk factors for incident diabetes defined by either FPG or HbA_{1c}; TG was an independent predictor for incident A1C-DM alone, and elevated blood pressure and sibling history of diabetes were independent predictors of incident FPG-DM alone. In these multivariate models, age was significantly and negatively associated with incident A1C-DM, FPG-DM, or FPG/A1C-DM. HbA_{1c} was positively associated with incident FPG-DM. HbA_{1c} was also associated negatively when <4.66% and positively when >4.66% with incident A1C-DM, as the quadratic function of HbA_{1c} in the model decreased when HbA_{1c} was <4.66% and increased when >4.66%. Similarly, for incident FPG/A1C-DM, the inflection point of HbA_{1c} was 4.73%. UACR was associated negatively when UACR was <1 and positively when UACR was >1 with incident diabetes by all three criteria, as the function Log (UACR) × Log(UACR) was decreased when UACR was <1 and increased when UACR was >1.

The AROC was 0.75 ($P < 0.0001$) from the predictive model of incident A1C-DM, indicating good discrimination ability. The Hosmer-Lemeshow statistic of the model was 11.23 ($P = 0.1889$), indicating good calibration. The respective figures were 0.77 ($P < 0.0001$) and 8.30 ($P = 0.4048$) from the predictive model of incident FPG-DM and 0.71 ($P < 0.0001$) and 10.36 ($P = 0.2407$) from the predictive model of incident FPG/A1C-DM. The internal validation results using the bootstrapping method yielded a bootstrap-corrected AROC and *P* value of the Hosmer-Lemeshow statistic of 0.74 and 0.2585, respectively, from the predictive model of incident A1C-DM, indicating high reliability of discrimination and calibration. The respective figures were 0.76 and 0.5248 from the predictive model of incident FPG-DM and 0.70 and 0.3261 from the

Table 2—*Comparison of risks of A1C-DM, FPG-DM, or FPG/A1C-DM in 4 years among subgroups of each risk factor after adjusting for age, sex, and center: the SHS*

	A1C-DM			FPG-DM			FPG/A1C-DM		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
FPG (mg/dL)									
IFG vs. NFG				3.12	2.31–4.22	**<0.0001**	2.34	1.81–3.03	**<0.0001**
HbA$_{1c}$ (%)									
6.0–6.4 vs. <6.0	5.89	4.23–8.19	**<0.0001**				3.43	2.27–5.16	**<0.0001**
JNC-7 HTN status									
Pre-HTN vs. normal	1.13	0.85–1.51	0.4076	1.50	1.09–2.05	**0.0119**	1.33	1.00–1.77	**0.0491**
HTN vs. normal	1.54	1.15–2.07	**0.0035**	1.63	1.17–2.26	**0.0036**	1.40	1.04–1.90	**0.0270**
Obesity status									
Overweight vs. normal	1.40	0.94–2.09	0.0962	1.57	0.99–2.51	0.0564	1.50	1.01–2.23	**0.0420**
Obese vs. normal	2.66	1.83–3.88	**<0.0001**	3.73	2.41–5.77	**<0.0001**	2.99	2.05–4.34	**<0.0001**
Obese vs. overweight	1.90	1.46–2.47	**<0.0001**	2.37	1.76–3.19	**<0.0001**	1.98	1.53–2.58	**<0.0001**
Parental history of diabetes (yes vs. no)	1.63	1.25–2.12	**0.0003**	1.22	0.92–1.62	0.1735	1.32	1.02–1.72	**0.0369**
Sibling history of diabetes (yes vs. no)	1.58	1.26–2.00	**0.0001**	1.64	1.27–2.11	**0.0001**	1.42	1.12–1.80	**0.0040**
Albuminuria									
Micro- vs. normal	1.97	1.39–2.80	**0.0001**	2.69	1.88–3.85	**<0.0001**	2.38	1.66–3.40	**<0.0001**
Macro- vs. normal	1.93	0.98–3.80	0.0557	2.43	1.26–4.70	**0.0083**	1.27	0.56–2.84	0.5682
Metabolic syndrome traits (yes vs. no)									
Elevated blood pressure	1.56	1.23–1.99	**0.0003**	1.68	1.29–2.18	**0.0001**	1.56	1.22–1.99	**0.0003**
HyperTG	1.51	1.19–1.93	**0.0009**	1.61	1.23–2.10	**0.0005**	1.54	1.20–1.98	**0.0008**
LowHDL-C	1.51	1.19–1.90	**0.0006**	1.61	1.24–2.08	**0.0003**	1.55	1.22–1.96	**0.0003**
HighWAIST	2.61	1.92–3.56	**<0.0001**	3.88	2.69–5.59	**<0.0001**	2.43	1.79–3.30	**<0.0001**

The risk-factor data from the baseline exam and the incident diabetes status data from the second exam collected from participants without A1C-DM, FPG-DM, or FPG/A1C-DM at the baseline exam were used to obtain the results for cumulative incident A1C-DM, FPG-DM, and FPG/A1C-DM, respectively. Albuminuria = normal, UACR <30 mg/g; micro-, 30 ≤ UACR < 300 mg/g; and macro-, 300 mg/g ≤UACR. FPG-DM = diabetes, FPG ≥126 mg/dL or on diabetes medications; IFG, 100 ≤ FPG < 126 mg/dL; and NFG, FPG <100 mg/dL. FPG/A1C-DM = diabetes, FPG ≥126 mg/dL or HbA$_{1c}$ ≥6.5%, or on diabetes medications; nondiabetic otherwise. Obesity = normal, BMI <25 kg/m^2; overweight, 25 ≤ BMI < 30 kg/m^2; obese, BMI ≥30 kg/m^2. A1C-DM = diabetes, HbA$_{1c}$ ≥6.5% or on diabetes medications; nondiabetic otherwise. JNC-7 HTN status = normal, SBP <120 mmHg and DBP <80 mmHg; Pre-HTN, 120 ≤ SBP < 140 mmHg and DBP <90 mmHg, or SBP <140 and 80 ≤ DBP < 90 mmHg; HTN, SBP ≥140 or DBP ≥90 or on HTN medications. Metabolic syndrome traits = elevated blood pressure, SBP ≥130 mmHg, DBP ≥85 mmHg, or on HTN medications. highWAIST = WAIST >102 cm in men or >88 cm in women. hyperTG = TGs ≥150 mg/dL. lowHDL-C = HDL-C <40 mg/dL in men or <50 mg/dL in women. Data in bold are significant.

predictive model of incident FPG/A1C-DM.

The predictive model for incident FPG/A1C-DM using both FPG and HbA$_{1c}$ at the baseline was significantly better than the predictive model for incident FPG/A1C-DM obtained by the same selecting procedures but without considering the baseline HbA$_{1c}$ (P = 0.0216), or the one without considering the baseline FPG (P = 0.0118) (data not shown). Risk calculators based on these proposed models are provided on the SHS Web site for general public, clinical physicians, or study investigators.

CONCLUSIONS—We found that using HbA$_{1c}$ alone in an initial diabetes screening among undiagnosed adults in a population-based sample identified fewer cases of prevalent diabetes than using FPG alone (Table 1). However, for identifying cases of prevalent diabetes in a 4-year periodic successive diabetes screening or identifying incident diabetes in 4 years in undiagnosed participants, each criterion missed cases of diabetes identified by the other (Table 1). We also showed that using both HbA$_{1c}$ and FPG identified a larger group of people at risk.

The discordances between diabetes identified by HbA$_{1c}$ and glucose criteria were also found in U.S. 2003–2006 National Health and Nutrition Examination Survey data (18) and in several other studies in different ethnic groups (19). In general, HbA$_{1c}$ detected lower prevalence of diabetes than glucose criteria in U.S. and other populations, especially in undiagnosed participants (4,18,19), which is consistent with our findings in American Indians.

The discordances between diabetes identified by HbA$_{1c}$ and FPG among undiagnosed participants may be caused in part by the fact that HbA$_{1c}$ level reflects an integrated measure of glycemia over a 2- to 3-month period, whereas FPG reflects the influence of hepatic glucose output on the day of the visit (3,4,20).

We found that in the initial diabetes screening, among undiagnosed participants at the baseline exam FPG ≥126 mg/dL identified more cases of diabetes than HbA$_{1c}$ ≥6.5%, but in a successive diabetes screening 4 years later, among undiagnosed participants the percentages were equal. The difference between the initial and successive diabetes screenings may be because at the baseline exam those newly diagnosed participants might have had unrecognized diabetes for many years, while those newly diagnosed at the successive exam might have had unrecognized diabetes for at most 4 years. This supports the contention that HbA$_{1c}$ ≥6.5% represents sustained daily hyperglycemia sufficient to meaningfully influence glycation, whereas FPG ≥126 mg/dL may be a transient phenomenon that happens occasionally in many people. With a 4-year window, there is much less time to develop sustained hyperglycemia, and thus the two indicators are more comparable. Since in the usual clinical situation there

Table 3—*Predictive models for 4-year cumulated incidence of diabetes: the SHS*

		A1C-DM*				FPG-DM*				FPG/A1C-DM*			
	Unit	Coeff.	*P*	OR†	95% CI	Coeff.	*P*	OR†	95% CI	Coeff.	*P*	OR†	95% CI
Intercept		11.088	0.0076			−7.223	<0.0001			11.354	0.0049		
Age (years)	5	−0.033	0.0001	0.85	0.78–0.92	−0.033	0.0003	0.85	0.77–0.93	−0.029	0.0004	0.86	0.80–0.94
WAIST (cm)	10.0	0.011	0.0130	1.12	1.02–1.23					0.017	0.0003	1.18	1.08–1.30
highWAIST	1.0					0.770	<0.0001	2.16	1.52–3.14				
Elevated blood pressure	1.0					0.326	0.0263	1.39	1.04–1.85	0.286	0.0293	1.33	1.03–1.72
FPG (mg/dL)	10.0	0.028	<0.0001	1.33	1.23–1.44								
FPG × FPG						0.000	<0.0001			0.000	<0.0001		
HbA_{1c} (%)	0.5	−7.408	<0.0001			0.620	<0.0001	1.36	1.23–1.53	−6.480	<0.0001		
HbA_{1c} × HbA_{1c}		0.794	<0.0001							0.686	<0.0001		
Log(UACR) × Log(UACR)		0.021	0.0015			0.032	<0.0001			0.019	0.0047		
Log(TG)		0.332	0.0090										
hyperTG	1.0									0.372	0.0060	1.45	1.11–1.89
Sibling history of diabetes	1.0					0.342	0.0158	1.41	1.07–1.86				
AROC		0.75	<0.0001‡			0.77	<0.0001‡			0.71	<0.0001‡		
Hosmer–Lemeshow statistic		11.23	0.1889§			8.30	0.4048§			10.36	0.2407§		

The risk-factor data from the baseline exam and the incident diabetes status data from the second exam collected from participants without A1C-DM, FPG-DM, or FPG/A1C-DM at the baseline exam were used to obtain the predictive model for cumulative incident A1C-DM, FPG-DM, and FPG/A1C-DM, respectively. Variables in the models were selected according to the procedures explained in the statistical analyses section. Coeff., estimated regression coefficient. *See respective definitions in Table 2. †Related to the unit increment. ‡*P* value from testing whether AROC = 0.5. §*P* value from testing whether Hosmer–Lemeshow statistic = 0.

has not been a screening in the near past, the discrepancy between HbA_{1c} and FPG would likely prevail. The similar difference between the initial and successive diabetes screenings by using FPG and 2-h post plasma glucose was also reported in American Indians (21).

Our data show that a larger number of people at risk can be identified using both HbA_{1c} and FPG. One cost-effective diabetes screening procedure could be to *1*) measure HbA_{1c} for all participants and *2*) further measure FPG only for those participants with $4.75\% \leq HbA_{1c} < 6.5\%$, since our data show this would result in the identification of the most of remainder of those who would have diabetes by FPG criterion (Table 1). Others have also reported that using a method based on FPG and HbA_{1c} in diabetes screening was more efficient (21).

The final set of variables in our model for predicting incident diabetes was selected among those reported variables in the literature (11–13) plus AEHPW, years of education, current alcohol intake, HbA_{1c}, UACR, and additional interactions and nonlinear terms of these predictors. Each risk factor in the proposed models was associated significantly and independently to incident diabetes. Further studies are needed to see whether the risk-factor sets, independent contributions, and nonlinearity still hold if data from other populations are used. Prediction models for diagnosis using either criterion were similar, with major baseline variables including glycemia by either measure, obesity, WAIST, and UACR. Obesity and WAIST were important determinants; the latter, a reflection of abdominal fat, is closely associated with hyperinsulinemia and insulin resistance (22) and thus reflects the importance of insulin resistance as a determinant of type 2 diabetes. Glycemia, measured either by HbA_{1c} or FPG, depending on the model, was also an important determinant; it has been shown in many analyses that diabetes risk increases as glycemia increases within the nondiabetic range. Albuminuria measured by UACR, a renal marker of CVD and inflammation, is also an important determinant in all models, which is consistent with our previous demonstrations that albuminuria is an important risk factor for diabetes, HTN, and CVD in American Indians (6,23,24). The associations of HbA_{1c}, FPG, and Log(UACR) with incident diabetes were nonlinear, as evident by the quadratic forms of HbA_{1c}, FPG, and Log (UACR) entered instead of the primary variables in the predictive models. For HbA_{1c} this meant also that it changed directions from negative to positive association to incident diabetes at about HbA_{1c} = 4.7%. The reason why HbA_{1c} changed the direction of the association at about 4.7% was not clear and needs further study. Metabolic syndrome traits of elevated blood pressure and hyperTG also significantly predict incident diabetes in our models, similar to previous reports in the literature (12,25). This is likely because they also reflect insulin resistance.

The models for predicting incident A1C-DM, FPG-DM, or FPG/A1C-DM were all internally validated. The predictive model for incident FPG/A1C-DM using both FPG and HbA_{1c} at the baseline was significantly better than the model without considering the baseline FPG or HbA_{1c}.

This study has many strengths, including population-based sampling and systematic measures at two exams; further, this is a unique population that may become a reference for other populations with high rates of diabetes and diabetic CVD. Due to the high prevalence (~46%) of diabetes in American Indians, we are only able to use data collected from about half of 4,549 participants in the SHS cohort to derive predictive equations. Although our proposed models were internally validated, they should be tested and validated in other populations.

In conclusion, FPG and HbA$_{1c}$ criteria do not identify identical groups of individuals from a population-based sample as having diabetes. Using HbA$_{1c}$ alone to conduct an initial diabetes screening in undiagnosed participants detects fewer cases of prevalent diabetes than FPG alone. However, for identifying cases of prevalent diabetes in a 4-year periodic successive diabetes screening or identifying cases of incident diabetes in 4 years in undiagnosed participants, using either FPG or HbA$_{1c}$ alone was not effective. Baseline FPG or HbA$_{1c}$ levels, WAIST, and UACR were common significant and independent risk factors for incident diabetes defined by either FPG- or HbA$_{1c}$-based criteria. Using both the baseline FPG and HbA$_{1c}$ to predict incident FPG/A1C-DM identified more people at risk. The proposed models can be applied to assess risk of incident A1C-DM, FPG-DM, or FPG/A1C-DM in American Indians and have potential applicability to other populations.

Acknowledgments—This study was supported by grants UO1 HL-41642, UO1 HL-41652, UO1 HL-41654, and U01-HL65521 from the National Heart, Lung, and Blood Institute.

No potential conflicts of interest relevant to this article were reported.

W.W. performed all analyses and wrote the manuscript; E.T.L, B.V.H., R.R.F., R B.D., and T.K.W. contributed to discussion and reviewed and edited manuscript.

The authors express their appreciation to the 13 participating American Indian tribes/communities, the Indian Health Service, and the participants for their support and assistance.

The authors also thank SHS field center coordinators Beverly Blake and Alan Crawford (SD/ND), Betty Jarvis (AZ), and Dr. Tauqeer Ali (OK) and the SHS staff for collecting the data.

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