Prediction of Type 2 Diabetes by Hemoglobin A_{1c} in Two Community-Based Cohorts

Aaron Leong,[1,2] Natalie Daya,[3] Bianca Porneala,[1] James J. Devlin,[4] Dov Shiffman,[4] Michael J. McPhaul,[4] Elizabeth Selvin,[3] and James B. Meigs[1,2]

https://doi.org/10.2337/dc17-0607

OBJECTIVE

Hemoglobin A_{1c} (HbA_{1c}) can be used to assess type 2 diabetes (T2D) risk. We asked whether HbA_{1c} was associated with T2D risk in four scenarios of clinical information availability: *1*) HbA_{1c} alone, *2*) fasting laboratory tests, *3*) clinic data, and *4*) fasting laboratory tests and clinic data.

RESEARCH DESIGN AND METHODS

We studied a prospective cohort of white (*N* = 11,244) and black (*N* = 2,294) middle-aged participants without diabetes in the Framingham Heart Study and Atherosclerosis Risk in Communities study. Association of HbA_{1c} with incident T2D (defined by medication use or fasting glucose [FG] ≥126 mg/dL) was evaluated in regression models adjusted for *1*) age and sex (demographics); *2*) demographics, FG, HDL, and triglycerides; *3*) demographics, BMI, blood pressure, and T2D family history; or *4*) all preceding covariates. We combined results from cohort and race analyses by random-effects meta-analyses. Subsidiary analyses tested the association of HbA_{1c} with developing T2D within 8 years or only after 8 years.

RESULTS

Over 20 years, 3,315 individuals developed T2D. With adjustment for demographics, the odds of T2D increased fourfold for each percentage-unit increase in HbA_{1c}. The odds ratio (OR) was 4.00 (95% CI 3.14, 5.10) for blacks and 4.73 (3.10, 7.21) for whites, resulting in a combined OR of 4.50 (3.35, 6.03). After adjustment for fasting laboratory tests and clinic data, the combined OR was 2.68 (2.15, 3.34) over 20 years, 5.79 (2.51, 13.36) within 8 years, and 2.23 (1.94, 2.57) after 8 years.

CONCLUSIONS

HbA_{1c} predicts T2D in different common scenarios and is useful for identifying individuals with elevated T2D risk in both the short- and long-term.

Since the adoption of hemoglobin A_{1c} (HbA_{1c}) as a biochemical diagnostic criterion for type 2 diabetes (T2D) by the International Expert Committee (IEC) in 2009 (1), by the American Diabetes Association (ADA) in 2010 (2), and by the World Health Organization in 2011 (3), HbA_{1c} is now used worldwide to screen for and diagnose T2D. Individuals with elevated HbA_{1c} levels in the nondiabetes range have been shown to be at elevated risk for developing T2D (4–7). Yet, international groups are not unanimous in their recommendations for the use of HbA_{1c} to screen for individuals with elevated T2D risk (8,9). For instance, the ADA and International Expert Committee recommend HbA_{1c} of 5.7–6.4% (39–46 mmol/mol) and 6.0–6.4% (42–46 mmol/mol), respectively, to identify prediabetes or an intermediate risk group, whereas the World Health Organization

[1]*Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA*
[2]*Harvard Medical School, Boston, MA*
[3]*John Hopkins Bloomberg School of Public Health, Baltimore, MD*
[4]*Quest Diagnostics, San Juan Capistrano, CA*

Corresponding author: James B. Meigs, jmeigs@mgh.harvard.edu.

Received 26 March 2017 and accepted 23 September 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0607/-/DC1.

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does not include HbA_{1c} among the recommended tests to identify individuals with elevated T2D risk (10).

Although fasting glucose (FG) has been the traditional method for assessing T2D risk, HbA_{1c} has several advantages: it reflects average glucose exposure over time, can be determined in nonfasting patients, has low intraindividual variability and low analytic variability (11–14), and has been standardized across laboratories worldwide (15). Despite these advantages, the utility of measuring HbA_{1c} for assessing T2D risk in various clinical and nonclinical settings has not been thoroughly evaluated. While it has been shown that the combination of both elevated FG and HbA_{1c} improved T2D prediction over FG alone (16), it remains uncertain whether measuring HbA_{1c}, as part of a comprehensive clinical assessment that includes laboratory testing of fasting individuals, provides additional information for T2D prediction. Alternatively, HbA_{1c} may be measured in settings where clinical information is limited, e.g., point-of-care testing at a medical center, pharmacy, or core or satellite chemistry laboratory. In these settings, HbA_{1c} is measured in either nonfasting or fasting blood, sometimes as part of a panel of laboratory tests, but usually without a thorough clinical evaluation of nonblood risk factors.

To address this knowledge gap, we tested the hypothesis that HbA_{1c} is associated with incident T2D independently of other risk factors assessed in several "real-world" scenarios. In the "HbA_{1c}-only" scenario, we evaluated the prediction of T2D based only on HbA_{1c}, age, and sex (i.e., assuming no other information was available, as might be obtained at point-of-care testing). In the "HbA_{1c} plus fasting laboratory tests" scenario, we assessed the value of measuring HbA_{1c} in addition to laboratory testing on fasting individuals, including FG, as might be the case in a comprehensive blood analysis. In the "HbA_{1c} plus clinic visit" scenario, we evaluated the value of adding HbA_{1c}, as the only laboratory test, to information available at a clinic visit. In the "HbA_{1c} plus fasting laboratory tests plus clinic visit" scenario, we assessed the value of adding HbA_{1c} to a clinic-based evaluation that included fasting laboratory testing (17). We evaluated these scenarios in middle-aged individuals without T2D who were followed for two decades for the development of T2D in two community-based cohorts: the Framingham Heart Study (FHS) (including white individuals) and the Atherosclerosis Risk in Communities study (ARIC) (including black and white individuals).

RESEARCH DESIGN AND METHODS

FHS and ARIC Study Populations

In FHS, the baseline examination (5th examination) was attended by 3,799 participants in the years 1992–1995. We excluded participants without measured baseline HbA_{1c} (N = 1,067), any of the other covariates (N = 20), or follow-up data (N = 179). We then excluded individuals who reported use of antidiabetes medications or who had FG $\geq$126 mg/dL or HbA_{1c} $\geq$6.5% ([48 mmol/mol) (N = 290). Our final study sample was 2,243 white participants. Excluded individuals had characteristics similar to those of included participants (Supplementary Table 1).

In ARIC, the baseline examination (2nd examination) was attended by 14,348 participants in the years 1990–1992. We excluded participants without measured missing baseline HbA_{1c} (N = 278) or any of the other covariates (n = 515). We then excluded individuals who, in baseline examinations, self-reported a physician diagnosis of T2D or use of antidiabetes medications or who had FG $\geq$126 mg/dL or HbA_{1c} $\geq$6.5% (48 mmol/mol) (N = 2,170). As only 91 participants self-identified as other than white or black, we were unable to examine other racial/ethnic groups in the U.S. Our final study sample was 9,001 white and 2,293 black participants.

The institutional review boards at each study site approved the study protocol, and written informed consent was obtained from all participants.

T2D Incidence

In FHS, incident T2D was defined as FG $\geq$126 mg/dL or start of antidiabetes therapy at any of four follow-up examinations over 19 years of follow-up (years 2011–2015). As physician-diagnosed T2D was not a standard question at these examination, we did not include it in the case definition. Follow-up time from the baseline examination (5th examination) was 4 years for the 6th examination, 7 years for the 7th examination, 13.5 years for the 8th examination, and 19 years for the 9th examination.

In ARIC, incident T2D was defined as FG $\geq$126 mg/dL, start of antidiabetes therapy, or self-reported physician diagnosis of T2D over a 22-year follow-up period (years 2012–2014). Follow-up time from the baseline examination (2nd examination) was 3 years for the 3rd examination, 6 years for the 4th examination, and 22 years for the 5th examination. Given the long interval between the fourth and fifth examinations, we also identified incident T2D cases by self-reported physician diagnosis of T2D or use of antidiabetes medications from annual telephone interviews for all participants.

Baseline Covariates

Physical examinations included measuring BMI and blood pressure in the sitting position. Self-reported information included race (white or black) and parental history of T2D. HbA_{1c} was measured in FHS using high-performance liquid chromatography after an overnight dialysis against normal saline to remove the labile fraction (18). HbA_{1c} was measured in ARIC using high-performance liquid chromatography, the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer method in 2003–2004, and the Tosoh G7 method in 2007–2008 (Tosoh Corporation) (4,19). All instruments were standardized to the Diabetes Control and Complication Trial assay (20). FG was measured using the hexokinase method in FHS and ARIC. HDL and triglycerides (TG) were determined using a commercially available assay (Hemagen Diagnostics, Inc, Waltham, MA) in FHS (21,22) and the Roche Cobas Bio analyzer (Roche Diagnostics, Basel, Switzerland) in ARIC (23).

Statistical Analyses

We performed the analyses in FHS, ARIC whites, and ARIC blacks separately. To display cumulative incidence of T2D by race, we generated Kaplan-Meier curves over the follow-up period, with time to event calculated from the baseline examination to the first diagnosis of incident T2D, death, loss to follow-up, or the last examination.

We constructed four primary prediction models to test the association of HbA_{1c} with incident T2D adjusted for covariates that represented the clinical information that would be available in four scenarios: *1*) The "HbA_{1c}-only" model was adjusted for age and sex. *2*) The "HbA_{1c} plus fasting laboratory tests" model was adjusted for age, sex, FG, HDL, and TG. *3*) The "HbA_{1c} plus clinic visit" model was adjusted for

age, sex, BMI, systolic blood pressure (SBP), and family history of T2D. And *4*) the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model was adjusted for age, sex, BMI, SBP, family history of T2D, FG, HDL, and TG (17). To fit these models, we used logistic regression in ARIC and generalized estimating equations that accounted for correlation within families in FHS. As HbA_{1c} in the nondiabetes range has a linear relationship with the log-odds of developing T2D (4), we modeled HbA_{1c} as a continuous variable.

To estimate the improvement in risk discrimination attributable to HbA_{1c}, we calculated differences in C statistics between the primary models and their respective nested models that included only the adjustment covariates but not HbA_{1c}. The C statistic is the probability that a model yields a higher predicted risk for a participant who did develop T2D than another who did not (24). The change in the C statistic when additional predictors are added to a model reflects their ability to improve risk prediction.

We used SAS (version 9.2 or 9.3; SAS Institute, Cary, NC) or Stata (version 13; StataCorp, College Station, TX) for all analyses. We considered a two-sided *P* value <0.05 to be statistically significant for the analysis that tested the primary hypothesis that HbA_{1c} predicts incident T2D in the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model.

We performed three sensitivity analyses. First, we repeated the primary analysis using HbA_{1c} modeled as a binary variable (HbA_{1c} 5.7–6.4% [39–46 mmol/mol] vs. HbA_{1c} <5.7% [39 mmol/mol]). Second, we repeated the analysis for the "HbA_{1c}-only" and "HbA_{1c} plus clinic visit" models using an alternative definition of T2D that included only self-reported physician diagnosis and antidiabetes medication use but not FG ≥126 mg/dL. Third, we repeated the analysis using another alternative definition that included self-reported physician diagnosis, antidiabetes medication use, FG ≥126 mg/dL, and HbA_{1c} ≥6.5% (48 mmol/mol).

Meta-analysis

As we noted heterogeneity between groups based on a Cochran *Q* statistic (25) ($P < 0.05$), we combined effect estimates from our primary models across all three groups using DerSimonian and Laird random-effects meta-analyses that accounted for both within-group and between-group variability (26)

Secondary Analyses

First, we conducted secondary analyses to investigate whether HbA_{1c} was associated with developing T2D in both the short- and long-term. To estimate the short- and long-term risk of T2D, we performed multinomial logistic regression to test the association of HbA_{1c} with incident T2D modeled as a three-level outcome variable, i.e., no T2D over the follow-up period, incident T2D within the first 8 years, and incident T2D only after 8 years and up to two decades. To account for familial correlation in FHS, we performed mixed-effects multinomial logistic regression. Second, to determine whether HbA_{1c} was associated with incident T2D in both those with and those without impaired FG (IFG), we performed stratified analyses by FG ≥100 mg/dL vs. FG <100 mg/dL.

Absolute Risk Estimation

The concept of absolute T2D risk associated with a specific HbA_{1c} value may be more clinically useful and easily conceptualized by some patients compared with relative risk. Absolute risks can be reported to patients to define personal risk and be compared with population-normative standards to identify actionable thresholds. To do this, we pooled data from FHS and ARIC and generated predicted probabilities of incident T2D (i.e., absolute risks) from a logistic regression model that adjusted HbA_{1c} for race, cohort, age, and sex. We also generated the predicted probabilities of developing T2D over the short-term and long-term using multinomial logistic regression on the three-level outcome variable.

We displayed the predicted probabilities using box plots by 11 HbA_{1c} levels of 0.2%-point increments from 4.5–6.5% (26–48 mmol/mol) to identify HbA_{1c} levels with predicted risk probabilities that were higher than the average risk of incident T2D in middle-aged adults in the U.S., defined by the annual incidence of diagnosed T2D for U.S. adults aged 45–64 years in 2014, estimated by the Centers for Disease and Control Prevention at 10.5 per 1,000 persons (27). Thus, we defined high risk as a predicted probability of T2D ≥0.21 (20 * 10.5/1,000 = 0.21) over 20 years or >0.08 (8 * 10.5/1,000 = 0.08) over the first 8 years.

As FG and HbA_{1c} can be measured concurrently for the purpose of T2D risk assessment, we sought to estimate the absolute risk of T2D associated with various combinations of HbA_{1c} and FG values. We first generated predicted probabilities of incident T2D from a logistic regression model that additionally adjusted HbA_{1c} for FG. We then displayed the predicted probabilities using box plots by a 12-category HbA_{1c}-FG variable defined by the combinations of three levels of FG variable (<100, 100–110, and ≥110 mg/dL) and four levels of HbA_{1c} (<5.4, 5.4–5.7, 5.7–6.0, and ≥6% [<36, 36–39, 39–42, and ≥42 mmol/mol]). We selected these FG and HbA_{1c} cut points to reflect the prediabetes thresholds recommended by the ADA (HbA_{1c} ≥5.7% [39 mmol/mol] and FG ≥100 mg/dL) (28), and other international groups (HbA_{1c} ≥6% [42 mmol/mol] and FG ≥110 mg/dL) (8,10,29,30). We included an additional HbA_{1c} cut point defined by the median of the distribution for HbA_{1c} (5.4% [36 mmol/mol]) to represent a low-normal HbA_{1c}. As above, categories that had predicted probabilities that were higher than the average risk of incident T2D in middle-aged adults in the U.S. were considered high risk for T2D. To assess how HbA_{1c} cut points 5.4, 5.7, and 6.0% (36, 39 and 42 mmol/mol) may contribute to deciding whether a patient is at high risk for T2D, we estimated positive predictive values (PPV) for rule-in decisions and negative predictive values (NPV) for rule-out decisions.

RESULTS

Participants who developed T2D had higher BMI, SBP, TG, FG, and HbA_{1c} and lower HDL and were more likely to have a T2D family history compared with those who did not develop T2D. ARIC blacks had a slightly higher proportion of women and higher BMI and HbA_{1c} than ARIC whites (Table 1). In all four models, each 1%-unit increase in HbA_{1c} was associated with a 2.7- to 4.5-fold higher incidence of T2D in FHS whites, ARIC whites, and ARIC blacks, as well as in the meta-analysis of these three groups (Fig. 1 and Supplementary Tables 2 and 3 [for all models we provided the full model regression equations]). Results were similar when the analysis was repeated using either HbA_{1c} modeled as a binary variable (Supplementary Table 4) or the alternative T2D definitions that excluded FG (Supplementary Table 5) or additionally included HbA_{1c} ≥6.5% (Supplementary Table 6).

Table 1—Characteristics of participants in FHS and ARIC by incident T2D status at follow-up

	FHS (N = 2,243), baseline years 1991–1995			ARIC whites (N = 9,001), baseline years 1990–1992			ARIC blacks (N = 2,293), baseline years 1990–1992		
	No incident T2D	Incident T2D	*P*	No incident T2D	Incident T2D	*P*	No incident T2D	Incident T2D	*P*
N (%)	1,973 (88.0)	270 (12.0)		6,719 (74.6)	2,282 (25.4)		1,530 (66.7)	763 (33.3)	
Age (years), mean (SD)	54.3 (10)	55.4 (9.4)		57.3 (5.7)	56.4 (5.4)	*	56.2 (5.9)	55.1 (5.5)	*
Female (%)	56.2	47.8	*	55.0	51.7	*	62.6	64.4	
BMI (kg/m^2), mean (SD)	26.7 (4.5)	30.4 (5.0)	*	26.3 (4.4)	28.7 (5.0)	*	28.5 (5.9)	30.7 (6.1)	*
SBP (mmHg), mean (SD)	123.5 (18)	133.5 (18.6)	*	117.8 (17.3)	121.0 (17.2)	*	125.8 (20.9)	126.1 (20.3)	
HDL (mg/dL), mean (SD)	52.2 (15.2)	42.6 (12.9)	*	51.1 (16.8)	45.4 (15.0)	*	56.3 (17.7)	52.5 (16.3)	*
Fasting TG (mg/dL), mean (SD)	132.4 (82.6)	190.2 (105.5)	*	125.8 (67.5)	156.9 (96.1)	*	97.1 (48.5)	116.8 (91.3)	*
Fasting glucose (mg/dL), mean SD	93.6 (8.7)	104.6 (9.6)	*	99.6 (8.5)	105.4 (9.7)	*	101.0 (9.1)	106.5 (9.9)	*
HbA_{1c} (%-points), mean (SD)	5.2 (0.5)	5.5 (0.5)	*	5.3 (0.3)	5.5 (0.4)	*	5.5 (0.4)	5.7 (0.4)	*
Family history of diabetes (%)	15.3	26.7	*	18.6	28.9	*	21.6	26.9	*
Follow-up time (years), median/mean (SD)	18.2/15.3 (5.3)	6.5/9.1 (5.9)	*	21.0/18.3 (5.1)	13.1/12.7 (5.7)	*	21.1/17.5 (5.9)	12.1/12.3 (5.5)	*

We excluded from this analysis individuals who, in baseline examinations, self-reported a physician diagnosis of T2D or use of antidiabetes medications or had FG ≥126 mg/dL or HbA_{1c} ≥6.5% (48 mmol/mol) at baseline. To convert FG to mmol/L, multiply by 0.0555; to convert cholesterol to mmol/L, multiply by 0.0259; and to convert TG to mmol/L, multiply by 0.0113. Race was self-reported; BMI is the weight in kilograms divided by the square of height in meters. Follow-up time was calculated from the baseline examination to the first diagnosis of incident T2D at an examination visit or in a telephone survey, at death, at last appearance at an examination visit, or at the last examination visit. *$P < 0.05$ for *t* tests and χ^2 tests, which test for differences in baseline characteristics between those who developed T2D and those who did not in FHS, ARIC whites, and ARIC blacks.

While the association between HbA_{1c} and incident T2D in ARIC differed according to race in the "HbA_{1c}-only" model ($P_{interaction} = 0.01$), there was no difference after adjustment for other covariates in the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model (*P* interaction = 0.11) (Supplementary Table 7). Kaplan-Meier curves showed clear separation of the curves for HbA_{1c} ≥5.7% (39 mmol/mol) vs. <5.7% (39 mmol/mol) in blacks (ARIC) and whites (pooled across ARIC and FHS) (log-rank $P < 0.001$) (Fig. 2). Incidence of T2D was similar between blacks and whites with HbA_{1c} >5.7% (39 mmol/mol) (log-rank $P = 0.25$).

In FHS, HbA_{1c} improved the predictive performance in the "HbA_{1c}-only" model and "HbA_{1c}-clinic visit" model (difference in C statistic, $P < 0.05$). In ARIC, HbA_{1c} improved the predictive performance in all four models and in both races (difference in C statistic, $P < 0.001$) (Table 2). Addition of clinical predictors from the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model to a base model with only HbA_{1c} improved its predictive performance significantly ($P < 0.05$) (Supplementary Table 8).

In all four models, higher HbA_{1c} was associated with increased T2D risk in both participants with and without IFG. Among FHS whites, ARIC whites, and ARIC blacks with IFG, the meta-analytic odds ratio (OR) for the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model was 3.14 (95% CI 2.67, 3.69) per 1%-unit increase. Among those without IFG, the meta-analytic OR was 2.20 (95% CI 1.68, 2.88) per 1%-unit increase (Supplementary Table 9). HbA_{1c} improved the predictive performance when added to each of the four models in FHS whites, ARIC whites, and ARIC blacks with IFG (difference in C statistic, $P < 0.05$) (Supplementary Table 10).

In secondary analyses, higher HbA_{1c} was associated with higher T2D risk both in the short-term (within 8 years of the baseline visit) and in the long-term (T2D incidence >8 years after the baseline visit). The meta-analytic OR for the "HbA_{1c} plus fasting laboratory tests plus clinic visit" model was 5.79 (95% CI 2.51, 13.36) per 1%-unit increase for short-term T2D and 2.23 (95% CI 1.94, 2.57) for long-term T2D (Supplementary Table 11).

Higher HbA_{1c} was associated with higher absolute risk for incident T2D over the 20-year follow-up period (Fig. 3*A*). Likewise, the predicted absolute risk

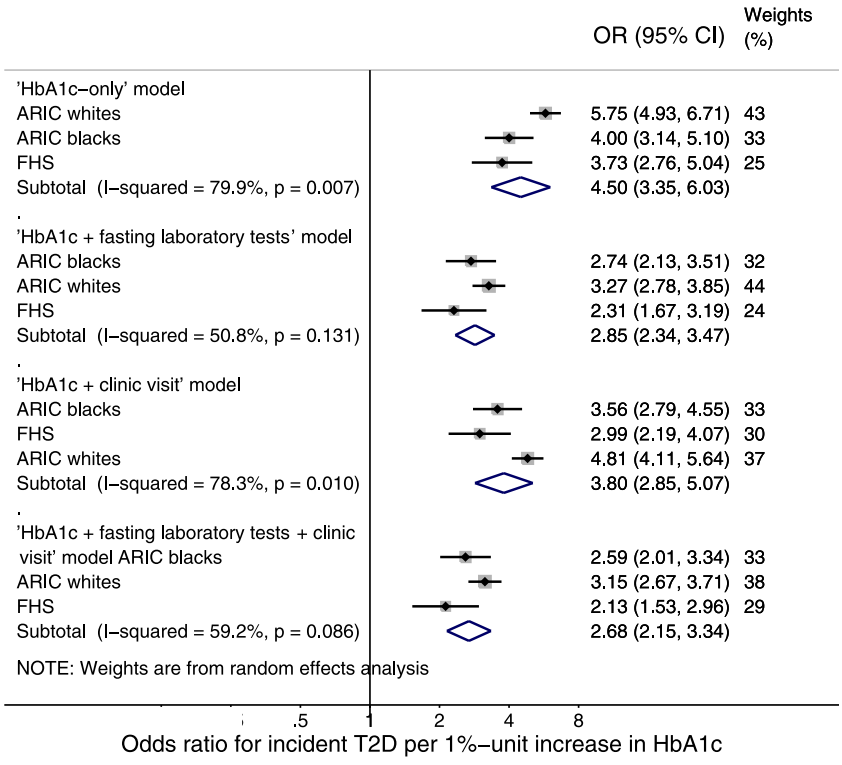

Figure 1—Association of HbA_{1c} with incident T2D over two decades adjusted for other clinical predictors by cohort and race. In all four models, each 1%-unit increase in HbA_{1c} was associated with a 2.7- to 4.5-fold higher incidence of T2D in FHS whites, ARIC whites, and ARIC blacks, as well as in the meta-analysis of these three groups. "HbA_{1c}-only" model: adjusted for age and sex; "HbA_{1c} + fasting laboratory tests" model: adjusted for age, sex, FG, TG, and HDLs; "HbA_{1c} + clinic visit" model: adjusted for age, sex, SBP, family history of T2D, and BMI; "HbA_{1c} + fasting laboratory tests + clinic visit" model: adjusted for age, sex, FG, TG, HDLs, SBP, family history of T2D, and BMI. As we observed heterogeneity in the effect estimates, we performed the meta-analysis using random effects. OR, OR per 1%-unit increase in HbA_{1c}; I-squared, Higgins I^2 test for heterogeneity. (A high-quality color representation of this figure is available in the online issue.)

increased in a graded fashion with higher HbA_{1c} values over both short-term (within 8 years) and long-term (only after 8 years) follow-up (Fig. 3*B*). The predicted absolute risk of T2D over the 20-year follow-up period was higher for each successive HbA_{1c} level (<5.4, 5.4–5.7, 5.7–6.0, and ≥6.0%) within each FG level (<100, 100–109, and ≥110 mg/dL) (Fig. 3*C*). In Fig. 3*D*, the 75th percentile of predicted probabilities was <0.08 for all HbA_{1c}-FG categories with HbA_{1c} <5.4%, indicating that >75% of participants with HbA_{1c} <5.4% had less-than-average 8-year risk regardless of FG level.

HbA_{1c} levels of ≥5.4% (36 mmol/mol), ≥5.7% (39 mmol/mol), and ≥6.0% (42 mmol/mol) had PPV of 90%, 97%, and 99% and NPV of 78%, 56%, and 46%, respectively, for being at above-average 20-year risk and PPV of 51%, 89%, and 100% and NPV of 100%, 94%, and 80%, respectively, for being at above-average 8-year risk. After we accounted for FG, HbA_{1c} levels of ≥5.4% (36 mmol/mol), ≥5.7% (39 mmol/mol), and ≥6.0% (42 mmol/mol) had PPV of 72%, 86%, and 93% and NPV of 76%, 63%, and 69%, respectively, for above-average 20-year risk and PPV of 40%, 59%, and 78% and NPV of 94%, 88%, and 81%, respectively, for above-average 8-year risk (Supplementary Table 12).

CONCLUSIONS

While previous epidemiologic studies have shown that higher HbA_{1c} levels are associated with higher T2D risk in multiple ethnic populations around the world (5,31–44), the value of HbA_{1c} has not been comprehensively evaluated for absolute risk in the distinct real-world scenarios in which HbA_{1c} is most often used. In this study of two large, community-based populations, we tested whether HbA_{1c} had practical utility for T2D prediction and risk stratification in four common scenarios. We showed that HbA_{1c} was associated with approximately two- to fourfold greater risk for incident T2D per 1%-unit increase in each of the four scenarios tested: *1*) HbA_{1c} plus age and sex, *2*) HbA_{1c} and other fasting laboratory tests, *3*) a clinical assessment without any other laboratory testing except for HbA_{1c}, and *4*) a comprehensive clinical assessment that included HbA_{1c} in addition to other fasting laboratory tests. We thus confirmed that HbA_{1c} predicts future T2D independently of multiple clinical predictors, including FG, that are routinely collected in clinical and nonclinical settings (4).

In the Coronary Artery Risk Development in Young Adults study, HbA_{1c} modestly improved the predictive performance of a model composed of clinical and fasting laboratory test variables in both black and white participants followed for 5 years (45). Here, we showed that HbA_{1c} was strongly associated with higher T2D risk in both black and white participants from FHS and ARIC who were followed for two decades. Our analysis of short-and long-term risk implied that the elevated risk of developing T2D associated with a higher HbA_1 extends well beyond 8 years even if an individual remains T2D free in the short-term in each of the scenarios tested.

To assess the ability for HbA_{1c} to predict T2D at the population level over other clinical predictors, we calculated the difference in C statistic after adding HbA_{1c} to models composed of covariates representing the available information in each of the four scenarios. We showed that HbA_{1c} significantly improves the identification of individuals who are more likely than others from the population to develop T2D even when demographic and nonblood predictors have been obtained. The improvement is, however, minimal when fasting laboratory test measures have also been obtained. Nevertheless, in clinical situations where the status of a specific patient's risk factors (including FG) are known, HbA_{1c} remains a strong independent predictor of T2D where each 1%-unit increase in HbA_{1c} is associated with a two- to threefold T2D risk. This higher risk of developing T2D in the next 20 years associated with a 1%-unit increase in HbA_{1c} can be communicated to patients to motivate strategies for T2D prevention.

T2D screening and prediction in people without overt symptoms of hyperglycemia has potential value for early detection and treatment that, in turn, may

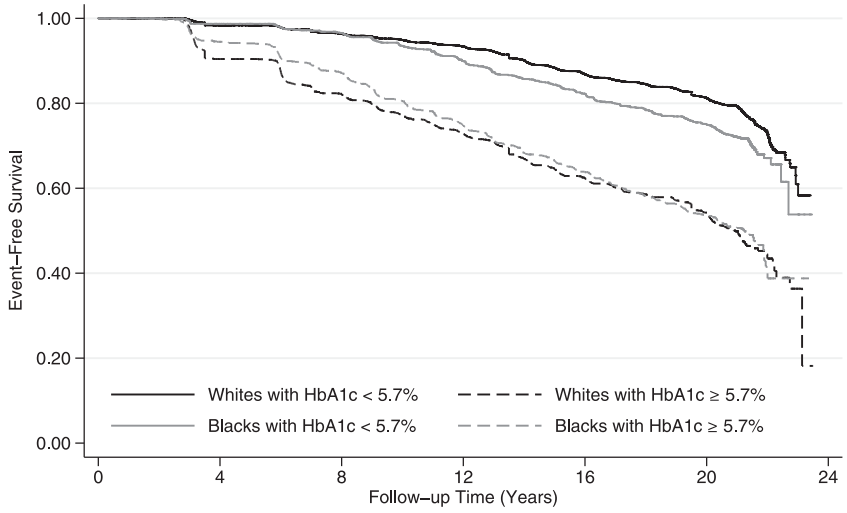

Figure 2—Incidence of T2D over a two-decade follow-up period in FHS and ARIC by HbA_{1c} (≥5.7% [39 mmol/mol] vs. <5.7% [39 mmol/mol]) and race (blacks and whites). Kaplan-Meier curves showed clear separation of the curves for HbA_{1c} ≥5.7% (39 mmol/mol) vs. <5.7% (39 mmol/mol) in blacks (ARIC) and whites (pooled across ARIC and FHS). While the incidence of T2D among those with HbA_{1c} <5.7% (39 mmol/mol) was higher in blacks (14.5 events per 1,000 person-years [95% CI 12.9, 16.2]) than whites (10.6 events per 1,000 person-years [95% CI 10.1, 11.1]; log-rank test $P <$ 0.0001), incidence of T2D among those with HbA_{1c} ≥5.7% was similar between blacks (30.5 events per 1,000 person-years [95% CI 28.6, 32.5]) and whites (29.4 events per 1,000 person-years [95% CI 26.8, 32.1]; log-rank test $P = 0.25$).

reduce T2D-related complications (5,46,47). We have demonstrated that HbA_{1c} has high predictive performance for incident T2D and is therefore effective for identifying high-risk individuals so that preventive measures can be targeted at those who may need them the most. Our results show that HbA_{1c} is an independent predictor of T2D in people with strictly normal FG and in people with IFG, suggesting that measuring HbA_{1c} in addition to FG may further improve risk assessment. While FG and HbA_{1c} individually have high predictive performance for incident T2D in longitudinal studies (5,31–38), current clinical cut points for HbA_{1c} or FG alone have low sensitivity for detecting T2D and prediabetes defined by oral glucose tolerance tests in cross-sectional examinations (48,49). Nevertheless, FG and HbA_{1c} are highly preferred over oral glucose tolerance tests as screening tests because of their ease of administration, greater acceptability to patients, and lower cost and clear predictive ability for long-term clinical outcomes (10).

As the association of HbA_{1c} with T2D risk is observed across the entire spectrum of the nondiabetes range of HbA_{1c} (4), suitable thresholds to define prediabetes continue to be debated (50). In this investigation, we evaluated HbA_{1c} cutoffs ≥5.7% (39 mmol/mol) and ≥6.0% (42 mmol/mol) for their ability to identify individuals with elevated 20-year T2D risk and found that these thresholds had high PPV for elevated risk with and without accounting for FG but only mediocre NPV, suggesting that applying these thresholds would effectively "rule in" but not "rule out" high 20-year T2D risk.

An advantage of measuring HbA_{1c} for risk stratification is in situations where a fasting blood sample for laboratory testing is not available or when overnight fasting is inconvenient, such as for patients who would need to return on a separate day for testing or travel great distances to test centers. Therefore, another effective use of HbA_{1c} would be to identify low-risk individuals who do not require fasting laboratory testing. While none of the three thresholds tested had high NPV to "rule out" individuals with high 20-year T2D risk, HbA_{1c} <5.4% (36 mmol/mol) had a high NPV to effectively "rule out" high 8-year T2D risk even after accounting for FG, implying that additional fasting laboratory testing to

Table 2—Improvement in predictive performance for incident T2D by adding HbA_{1c} to other covariates by cohort and race

Model	Covariates	Cohort/race	AUC without HbA_{1c} (95%CI)	AUC with HbA_{1c} (95%CI)	Difference in AUC (95% CI)	*P*
HbA_{1c} only	Age, sex	FHS	0.56 (0.53, 0.59)	0.68 (0.64, 0.72)	0.118 (0.076, 0.16)	<0.0001
		ARIC whites	0.55 (0.53, 0.56)	0.66 (0.65, 0.67)	0.113 (0.112, 0.114)	<0.0001
		ARIC blacks	0.55 (0.53, 0.58)	0.66 (0.63, 0.68)	0.106 (0.105, 0.107)	<0.0001
HbA_{1c} + fasting laboratory tests	Age, sex, FG, TG, HDL	FHS	0.85 (0.82–0.87)	0.85 (0.83, 0.88)	0.006 (−0.002, 0.014)	0.15
		ARIC whites	0.71 (0.70, 0.72)	0.73 (0.71, 0.74)	0.017 (0.017, 0.017)	<0.0001
		ARIC blacks	0.68 (0.66, 0.70)	0.71 (0.67, 0.73)	0.028 (0.028, 0.029)	<0.0001
HbA_{1c} + clinic visit	Age, sex, FH, BMI, SBP	FHS	0.75 (0.72–0.78)	0.77 (0.74, 0.80)	0.022 (0.005, 0.040)	0.013
		ARIC whites	0.67 (0.65, 0.68)	0.71 (0.70, 0.72)	0.042 (0.042, 0.042)	<0.0001
		ARIC blacks	0.62 (0.60, 0.65)	0.68 (0.66, 0.70)	0.058 (0.057, 0.059)	<0.0001
HbA_{1c} + fasting laboratory tests + clinic visit	Age, sex, BMI, SBP, FH, TG, HDL, FG	FHS	0.86 (0.83, 0.88)	0.86 (0.84, 0.89)	0.004 (−0.002, 0.011)	0.18
		ARIC whites	0.73 (0.72, 0.74)	0.74 (0.73, 0.75)	0.014 (0.013, 0.014)	<0.0001
		ARIC blacks	0.70 (0.673, 0.72)	0.72 (0.70, 0.74)	0.022 (0.022, 0.023)	0.001

AUC, area under the curve; FH, family history of T2D.

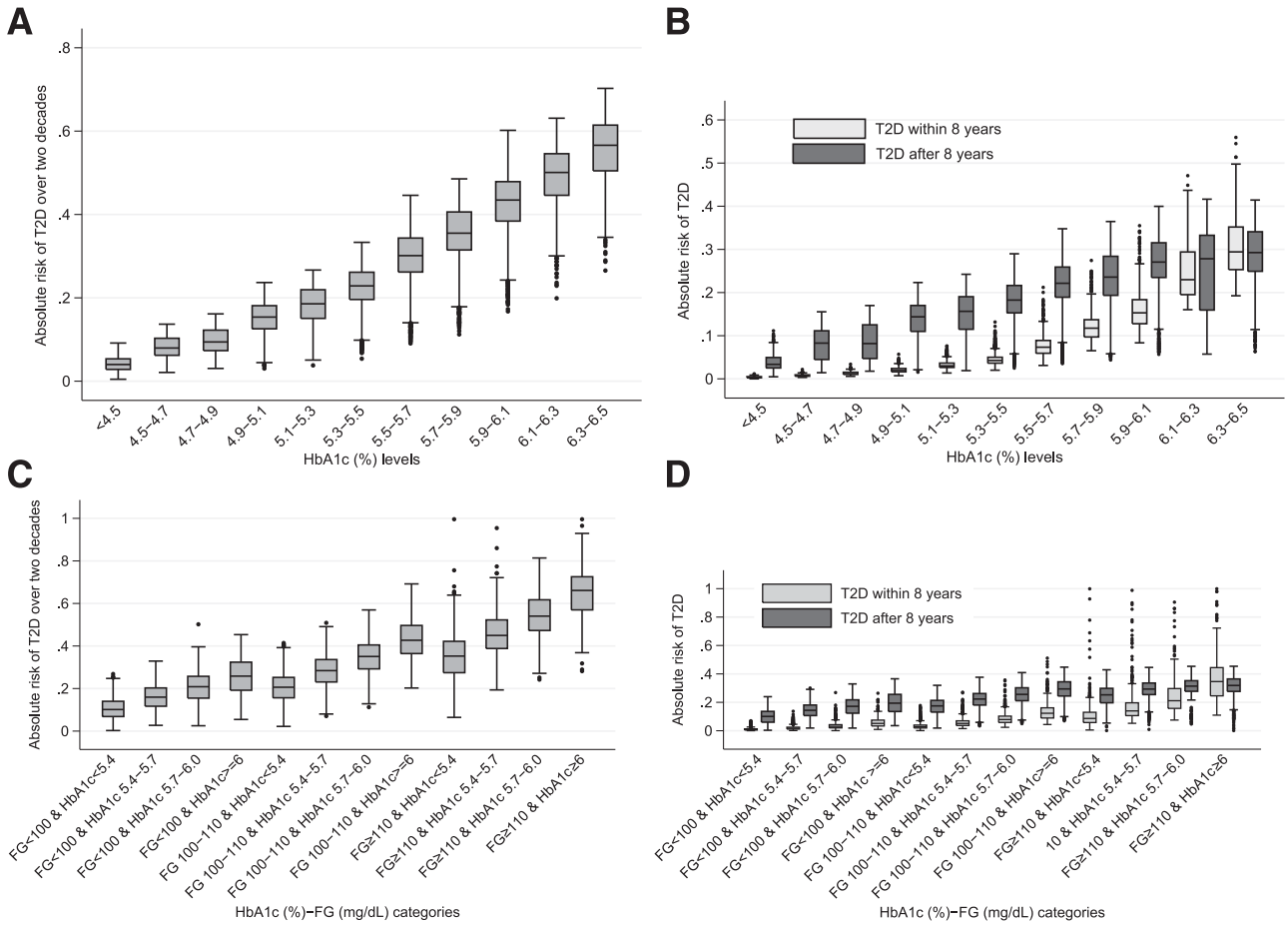

Figure 3—Absolute risks of incident T2D over two decades, within 8 years, and after 8 years by HbA_{1c} levels and HbA_{1c}-FG categories. *A*: HbA_{1c} (%) levels and T2D risk over two decades. *B*: HbA_{1c} (%)-FG (mg/dL) categories and T2D risk over two decades. *C*: HbA_{1c} (%) levels and T2D risk within 8 years and after 8 years. *D*: HbA_{1c} (%)-FG (mg/dL) categories and T2D risk within 8 years and after 8 years. *A*: Compared with lower HbA_{1c} levels, higher HbA_{1c} had higher predicted absolute risk for incident T2D over the 20-year follow-up period. *B*: Likewise, higher HbA_{1c} had higher predicted absolute risk for incident T2D over both short-term (within 8 years) and long-term (only after 8 years) follow-up. *C*: The predicted absolute risk over the 20-year follow-up period was higher with each successive HbA_{1c} level (<5.4, 5.4–5.7, 5.7–6.0, and ≥6.0% [<36, 36–39, 39–42, and ≥42 mmol/mol]) within each FG level (<100, 100–100, and ≥110 mg/dL). *D*: The predicted absolute risk period was higher with each successive HbA_{1c} level within each FG level over both short-term (within 8 years) and long-term (only after 8 years) follow-up. Regression models in *A* and *B* included HbA_{1c} age, sex, race, and cohort. Regression models in *C* and *D* included HbA_{1c}, FG, age, sex, race, and cohort. Box plots are represented by the first quartile (lower hinge) and median and third quartile (upper hinge) and whiskers indicating 1.5 times the interquartile range.

improve stratification of short-term T2D risk for these patients may be redundant and only incur unnecessary expense and inconvenience. Point-of-care HbA_{1c} testing during health maintenance visits may be adequate for these patients until their HbA_{1c} increases to 5.4% (36 mmol/mol) or above.

This study has several strengths. Our scenarios were constructed to be generic and therefore generalizable to different health systems that use HbA_{1c} for T2D prediction. As the risk estimates and prediction equations were obtained from large population-based cohorts of middle-aged adults from two major ethnicities in the U.S. with two decades of follow-up, they can be used in clinical laboratory reports, similar to the reporting of high values of prostate-specific antigen and LDL that are supplemented by their associated estimated risk for prostate cancer or cardiovascular disease.

We recognize several limitations. We elected to not include HbA_{1c} ≥6.5% (48 mmol/mol) in the case definition for T2D, as HbA_{1c} was only recommended for T2D diagnosis after 2010 and was not consistently measured in all follow-up examinations. We acknowledge that FG likely predicts FG-defined T2D better than HbA_{1c}. If HbA_{1c} were included in the case definition, we would expect HbA_{1c} to be an even better predictor of T2D than reported herein. Owing to small sample sizes, races/ethnicities other than whites and blacks (e.g., Asians, Hispanics, and Native Americans) were excluded from our analysis. We suggest caution in generalizing our findings to these other races/ethnicities. We do not address whether it is worth estimating T2D risk in older individuals or people with limited life expectancy, although we do include these people in our analysis. We do not specifically evaluate the value of estimating T2D risk in people with low baseline risk, i.e., lean adults aged <40 years, although such people were also included in our analysis. Our results are not relevant to people with conditions rendering HbA_{1c} inaccurate (e.g., anemia, renal failure, and some hemoglobinopathies) (51–53).

T2D continues to be a major public health problem. Given the evidence for prevention of T2D and its complications through intensive lifestyle intervention

or metformin (5,46), the importance of identifying high-risk individuals in diverse populations is paramount. Through this investigation, we show evidence supporting the use of HbA_{1c} for T2D prediction in two major racial groups of the U.S. We evaluated the utility of HbA_{1c} for identifying high- and low-risk individuals in a variety of common scenarios. HbA_{1c} is a useful tool for short-term and long-term risk prediction, in itself, and in situations where more clinical information, including fasting measures, is available. This accurate and convenient test has a central place in T2D prevention efforts nationally and worldwide.

Acknowledgments. The authors thank the staff and participants of ARIC and FHS for important contributions.

Funding. The FHS is supported by National Heart, Lung, and Blood Institute (NHLBI) contracts N01-HC-25195 and HHSN268201500001I. The ARIC study is carried out as a collaborative study supported by NHLBI contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The Asahi Kasei Corporation provided material support (kits only) for the glycated albumin assay used in this research. E.S. is supported in part by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grants K24-DK-106414 and R01-DK-089174. J.B.M. is supported in part by NIDDK K24-DK-080140.

Duality of Interest. Quest Diagnostics, Inc., supported this study. J.J.D., D.S., and M.J.M., from Quest Diagnostics, Inc., reviewed and commented on the manuscript but had no role in developing the scientific hypothesis or study design, performing the analysis, or compiling results. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.L. developed the scientific hypothesis, study design, and analysis plan; performed analyses; compiled results; and drafted the manuscript. N.D., B.P., E.S., and J.B.M. contributed to the scientific hypothesis, the study design, and analysis plan. N.D. and B.P. performed the analyses and compiled results. A.L., N.D., B.P., J.J.D., D.S., M.J.M., E.S., and J.B.M. reviewed all aspects of the manuscript and approved the final version of the manuscript. J.B.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017.

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