Elevated HbA_{1c} and Fasting Plasma Glucose in Predicting Diabetes Incidence Among Older Adults

Are two better than one?

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OBJECTIVE—To determine which measures—impaired fasting glucose (IFG), elevated HbA_{1c}, or both—best predict incident diabetes in older adults.

RESEARCH DESIGN AND METHODS—From the Health, Aging, and Body Composition study, we selected individuals without diabetes, and we defined IFG (100–125 mg/dL) and elevated HbA_{1c} (5.7–6.4%) per American Diabetes Association guidelines. Incident diabetes was based on self-report, use of antihyperglycemic medicines, or HbA_{1c} ≥6.5% during 7 years of follow-up. Logistic regression analyses were adjusted for age, sex, race, site, BMI, smoking, blood pressure, and physical activity. Discrimination and calibration were assessed for models with IFG and with both IFG and elevated HbA_{1c}.

RESULTS—Among 1,690 adults (mean age 76.5, 46% men, 32% black), 183 (10.8%) developed diabetes over 7 years. Adjusted odds ratios of diabetes were 6.2 (95% CI 4.4–8.8) in those with IFG (versus those with fasting plasma glucose [FPG] <100 mg/dL) and 11.3 (7.8–16.4) in those with elevated HbA_{1c} (versus those with HbA_{1c} <5.7%). When FPG and HbA_{1c} were considered together, odds ratios were 3.5 (1.9–6.3) in those with IFG only, 8.0 (4.8–13.2) in those with elevated HbA_{1c} only, and 26.2 (16.3–42.1) in those with both IFG and elevated HbA_{1c} (versus those with normal FPG and HbA_{1c}). Addition of elevated HbA_{1c} to the model with IFG resulted in improved discrimination and calibration.

CONCLUSIONS—Older adults with both IFG and elevated HbA_{1c} have a substantially increased odds of developing diabetes over 7 years. Combined screening with FPG and HbA_{1c} may identify older adults at very high risk for diabetes.

Diabetes Care 36:3923–3929, 2013

Impaired fasting glucose (IFG) (100–125 mg/dL) has been traditionally used for identifying persons at high risk for the subsequent development of diabetes in the U.S. Recent guidelines have additionally endorsed the use of HbA_{1c} 5.7–6.4% to identify those at risk (1). However, multiple studies, including one conducted among older persons (2), suggest that HbA_{1c} may identify different individuals at risk for diabetes than traditional glucose measures (3–6). Although several recent investigations confirm that HbA_{1c} is strongly predictive of future diabetes in predominantly middle-aged populations (7–10), less is known about how well HbA_{1c} identifies older persons at risk for diabetes.

Despite the high prevalence of type 2 diabetes in the elderly (10.9 million Americans in 2010) and the high incidence (390,000 new cases in 2010) of late-onset type 2 diabetes (>65 years) (11,12), there are few specific studies on prediction of diabetes in this group. One such study, based on an earlier Health, Aging, and Body Composition (Health ABC) analysis, developed a prediction rule for diabetes development, which included several factors: advanced age, female sex, elevated fasting plasma glucose (FPG), and triglyceride levels (13). However, HbA_{1c} was not examined as a potential predictor. In the Cardiovascular Health Study of men and women ≥65 years of age, BMI, waist-to-hip ratio, and weight gain were associated with a higher risk of diabetes, but the impact of glycemic measures on diabetes was not specifically examined (14). An Italian study of older adults (age 65–84 years) found that the combination of abnormal FPG (defined using World Health Organization [WHO] criteria: 110 to <126 mg/dL), increased waist circumference, and HbA_{1c} ≥7.0% increased the probability of incident diabetes roughly 14-fold (15). However, neither a direct comparison of current prediabetes categories (based upon FPG and HbA_{1c}) for prediction of diabetes nor an analysis of the utility of combined testing has previously been conducted in this population.

We therefore evaluated the odds for diabetes based upon baseline IFG and elevated HbA_{1c} among the participants of the longitudinal Health ABC study. We directly compared FPG- and HbA_{1c}-based criteria for predicting the eventual

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Received 18 December 2012 and accepted 27 June 2013.
DOI: 10.2337/dc12-2631
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-2631/-/DC1.

development of diabetes, and we evaluated the utility of combined testing for identifying older persons who develop diabetes. Since HbA_{1c} values are consistently higher in blacks compared with whites (3,16), we additionally explored race differences in diabetes prediction.

RESEARCH DESIGN AND METHODS

—Participants were from the Health ABC study, an ongoing longitudinal study that investigates changes in body composition as a common pathway by which multiple diseases contribute to disability. Participants (n = 3,075; 48.4% male and 41.6% black, aged 70–79 years) were recruited in 1997–1998 from Pittsburgh, Pennsylvania, and Memphis, Tennessee, using procedures previously described (17). A telephone interview determined eligibility using the following inclusion criteria: no difficulty performing activities of daily living, walking one-quarter of a mile or climbing 10 steps without resting; no reported need of assistive devices (e.g., cane, walker); no active treatment for cancer in the prior 3 years; no life-threatening illness; and no plans to leave the area for 3 years. Participants provided informed consent before examinations, and the study was approved by institutional review boards at the University of Pittsburgh and the University of Tennessee Health Science Center.

A National Glycohemoglobin Standardization Program (NGSP)-certified HbA_{1c} assay using modern chromatographic techniques was performed for the first time at the 2000–2001 follow-up (year 4), which served as the baseline visit for this analysis. Of the 3,075 participants in the Health ABC study, we excluded 187 who did not survive to baseline, 634 who had diagnosed diabetes (based on annual self-report from 1997 to baseline, the use of antihyperglycemic medication from 1997 to 1 year prior to baseline [medication use was not available at baseline], or HbA_{1c} ≥6.5% or FPG ≥126 mg/dL at our baseline visit), and 464 participants who had missing HbA_{1c} or FPG values at baseline. Finally, we also excluded participants without adequate follow-up after baseline, including 59 survivors who did not develop diabetes, but were missing at the final examination at year 7, and 41 participants who did not develop diabetes, died during follow-up, and missed the clinical visit within 1 year of death (because we could not determine whether they developed diabetes). Our final sample included 1,690 older adults.

Laboratory measurement of FPG and HbA_{1c}

HbA_{1c} was measured using Tosoh 2.2 Plus (Tosoh Bioscience, Tokyo, Japan), a fully automated glycosylated hemoglobin analyzer that uses nonporous ion-exchange high-performance liquid chromatography for separation of HbA_{1c}, with any labile glycohemoglobin subfractions chromatographically separated from the Shiff base. The HbA_{1c} assay was NGSP certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay method. FPG was measured after ≥8 h of fasting using the automated glucose oxidase method (VITROS system; Ortho Clinical Diagnostics, Rochester, NY).

Definition of outcome

The study outcome was a binary variable indicating whether a participant developed diabetes at any time between baseline and subsequent year 7 evaluation. Incident diabetes included new self-report of physician-diagnosed diabetes (obtained annually), the use of oral antihyperglycemic medications or insulin (available at visits at years 1, 2, 4, 6, and 7 of follow-up), or a single value of HbA_{1c} ≥6.5% collected at years 2, 6, and 7. Given that FPG was not repeated when obtained and given the known short-term variability in measures of FPG (18), we did not use FPG criteria to define our primary outcome.

Definition of main independent variables

Participants were classified as high risk for diabetes based upon two separate definitions: *1*) IFG (FPG 100–125 mg/dL) or *2*) elevated HbA_{1c} (5.7–6.4%). Participants were then categorized into four mutually exclusive groups: *1*) normal glucose tolerance, based on FPG <100 mg/dL and HbA_{1c} <5.7%; *2*) IFG only, based on FPG 100–125 mg/dL but HbA_{1c} <5.7%; *3*) elevated HbA_{1c} only, based on HbA_{1c} 5.7–6.4% but FPG <100 mg/dL; and *4*) both IFG and elevated HbA_{1c}, based on FPG 100–125 mg/dL and HbA_{1c} 5.7–6.4%.

Other measures

In addition to age, race, sex, and site (Pittsburgh vs. Memphis), several known risk factors for diabetes were assessed at baseline, including BMI, systolic blood pressure (average of two sitting systolic blood pressure measurements), and self-reported physical activity (weekly walking time). Smoking status was based on self-report and was available 1 year prior to baseline.

Statistical analysis

Multivariable logistic regression analyses were performed to estimate the odds ratios of incident diabetes (from baseline to year 7). The multivariable models were adjusted for age, sex, race, site, systolic blood pressure, BMI, smoking, and weekly walking time (none, <150 min/week, or ≥150 min/week).

To compare the odds of diabetes associated with each prediabetes category, we compared two models: first, IFG was compared with normal FPG (irrespective of HbA_{1c}), and second, elevated HbA_{1c} was compared with normal HbA_{1c} (irrespective of FPG). Discriminatory ability of each model was assessed using a *C* statistic with 95% CIs. Model fit was assessed with residual analysis and goodness-of-fit statistics.

To examine the odds of diabetes associated with the combination of the two tests, FPG and HbA_{1c}, we developed a model with three dummy-coded variables: IFG only, elevated HbA_{1c} only, and both IFG and elevated HbA_{1c} (individuals who had neither IFG nor elevated HbA_{1c} were the reference group), and we calculated odds ratios for these categories. Interaction terms crossing race and sex with the three dummy-coded predictor variables were added to the multivariable logistic regression model to assess race and sex as potential effect modifiers. Odds ratios for the different levels of the effect modifying variable were reported separately for race and sex.

To evaluate the utility of obtaining both tests (HbA_{1c} and FPG) for predicting diabetes, we compared the fully adjusted model containing IFG with a model that additionally contained elevated HbA_{1c}. The accuracy of each logistic regression model was assessed by examining both discrimination and calibration. Discrimination is the ability of the model to correctly distinguish those who develop the outcome (diabetes) from those who do not. This was calculated with a *C* statistic, which estimates the area under a receiver operating characteristic curve (AUC). The difference in the AUC between the two models was compared with the DeLong method (19). Because the *C* statistic is a rank-based statistic, it is very difficult for a new marker (in our case, elevated HbA_{1c})

to significantly change the value of AUC (20). Accordingly, two additional measures were used—Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI)—to provide additional information beyond AUC (21). IDI measures the incremental increase in the predicted probabilities for the subset experiencing an event (diabetes) and the incremental decrease for the subset not experiencing an event. The absolute IDI depends on the event rate observed and therefore may be small if events are rare, whereas relative IDI is a percentage. NRI evaluates the net number of individuals reclassified correctly as high versus low risk for diabetes using the model with elevated HbA_{1c} compared with the model without elevated HbA_{1c}. This is done by calculating how many individuals who developed diabetes increased in risk category and how many individuals who did not develop diabetes decreased in risk category. Finally, calibration was measured using the Hosmer-Lemeshow χ^2 test.

Sensitivity analyses. Additional analyses were performed with alternate definitions of the outcome: the first analysis was based on diabetes diagnosed by self-report only (available annually); the second was based on self-report or use of medications only (i.e., without the aid of diagnostic tests performed in the course of the study); the third was based on self-report, use of medications, FPG (≥126 mg/dL), or HbA_{1c} (≥6.5%); and the fourth was based on self-report, use of medications, or FPG (≥126 mg/dL). To address the timing of diabetes diagnosis, loss to follow-up, and death as a competing variable, we additionally analyzed the data using Cox proportional hazards regression and a Fine and Gray subdistribution hazards model (22) using the primary outcome of diabetes based on self-report, medication use, or HbA_{1c} ≥6.5%. In time-to-event models, we used the date of the clinic visit at which diabetes diagnosis was reported or laboratories were performed, and we censored participants at the time of death or at the last clinic visit when they contributed information about diabetes diagnosis.

An additional sensitivity analysis using the WHO definition of IFG, i.e., FPG 110–125 mg/dL, was also performed. When this definition is used, it is specified in the text; when unspecified, IFG refers to the American Diabetes Association (ADA) definition.

All analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC). *P* values <0.05 for two-sided tests are interpreted to indicate statistical significance.

RESULTS—Among the 1,690 participants during the baseline visit, the mean (SD) FPG was 92.8 mg/dL (9.5), and the median was 92.0 mg/dL (interquartile range 86–98). Respective values for HbA_{1c} were 5.3% (0.4) and 5.3% (5.1–5.6). The baseline characteristics of study participants are presented in Table 1. There were 779 (46.1%) men and 1,152 (68.2%) white participants in the present analysis. Of the study participants, 358 (21.2%) were identified as having IFG at baseline, 376 (22.2%) as having elevated HbA_{1c}, and 1,125 (66.6%) as having normal glucose tolerance (i.e., neither elevated FPG nor elevated HbA_{1c}). Among participants with dysglycemia, 189 (33.5%) had IFG only, 207 (36.6%) had elevated HbA_{1c} only, and 169 (29.9%) had both abnormalities.

Development of diabetes

From baseline to year 7, 183 (10.8%) participants developed diabetes based upon self-report, medication use, or HbA_{1c} ≥6.5%. Among the 183 participants with incident diabetes, 102 (55.7%) were white and 83 (45.4%) were men (Table 2). Black race and BMI were significantly associated with development of diabetes in bivariate analyses.

Among individuals with IFG (irrespective of HbA_{1c}) and elevated HbA_{1c} (irrespective of FPG) at baseline, 28.2 and 33.2% developed diabetes, respectively. In fully adjusted logistic regression models, the odds ratios for diabetes were 6.2 (95% CI 4.4–8.8) and 11.3 (7.8–16.4) in those with IFG and elevated HbA_{1c}, respectively. The c indices (for the two fully adjusted models with IFG and elevated

Table 1—*Baseline (2000–2001 visit) characteristics of the 1,690 participants*

	Total	Normal FPG and HbA_{1c}	IFG only	Elevated HbA_{1c} only	Both IFG and elevated HbA_{1c}
n	1,690	1,125	189	207	169
Age (years), mean (SD)	76.5 (2.9)	76.4 (2.8)	76.6 (3.0)	76.7 (3.0)	76.6 (2.8)
Sex (% men)	46.1	42.8	66.7	39.6	52.7
Race (% white)	68.2	72.9	82.0	36.2	60.4
Site (%)					
Pittsburgh	50.1	49.2	46.6	61.8	45.6
Memphis	49.9	50.8	53.4	38.2	54.4
SBP (mmHg), mean (SD)	140.3 (21.2)	139.8 (20.9)	142.6 (23.1)	141.8 (21.4)	139.5 (20.6)
BMI (kg/m^2), mean (SD)	27.0 (4.7)	26.4 (4.5)	27.9 (4.5)	27.9 (5.4)	29.0 (4.9)
Smoking (%)					
Current	7.1	7.6	4.4	7.1	6.3
Former	45.9	42.9	52.2	46.5	58.2
Walking time (%)					
None	43.4	41.2	46.3	50.7	46.4
<150 min/week	35.0	36.1	31.9	33.3	33.3
≥150 min/week	21.5	22.7	21.8	15.9	20.2
FPG (mg/dL), mean (SD)	92.8 (9.5)	88.4 (6.2)	105.3 (4.9)	92.3 (5.2)	108.7 (6.0)
HbA_{1c} (%), mean (SD)	5.3 (0.4)	5.2 (0.3)	5.3 (0.3)	5.8 (0.2)	5.9 (0.2)

SBP, systolic blood pressure.

Table 2—*Characteristics of participants who did and did not develop diabetes during follow-up*

	Diabetes at follow-up	No diabetes at follow-up	*P*
n	183	1,507	
Age (years), mean (SD)	76.1 (2.6)	76.5 (2.9)	0.061
Male sex (vs. female), *n* (%)	83 (45.4)	696 (46.2)	0.832
White race (vs. black), *n* (%)	102 (55.7)	1,050 (69.7)	<0.001
Pittsburgh site (vs. Memphis), *n* (%)	89 (48.6)	758 (50.3)	0.671
SBP (mmHg), mean (SD)	142.2 (21.3)	140.1 (21.2)	0.218
BMI (kg/m^2), mean (SD)	28.6 (4.4)	26.8 (4.7)	<0.001
Ever smoker (vs. never), *n* (%)	110 (60.1)	813 (54.0)	0.114
Walking time ≥150 min/week (vs. less), *n* (%)	38 (20.8)	325 (21.6)	0.803
Glycemic category, *n* (%)			
Normal FPG and HbA_{1c}	38 (20.8)	1,087 (72.1)	<0.001
IFG only	20 (10.9)	169 (11.2)	0.908
Elevated HbA_{1c} only	44 (24.0)	163 (10.8)	<0.001
IFG and elevated HbA_{1c}	81 (44.3)	88 (5.8)	<0.001

P values were calculated using χ^2 for categorical variables and *t* test for continuous variables. Percentages represent proportion of participants with and without diabetes who have a particular characteristic (e.g., 45.4% of participants who developed diabetes at follow-up were male). SBP, systolic blood pressure.

HbA_{1c}) were 0.76 (95% CI 0.72–0.79) and 0.81 (0.77–0.84), respectively.

When categorized into four mutually exclusive groups, diabetes developed in 3.4% of those with normal FPG and HbA_{1c}, 10.6% of those with IFG only, 21.3% of those with elevated HbA_{1c} only, and 47.9% of those with both IFG and elevated HbA_{1c} (*P* value for comparison across categories <0.001). In fully adjusted models, the odds ratios for diabetes were 3.5 (95% CI 1.9–6.3) in those with IFG only, 8.0 (4.8–13.2) in those with elevated HbA_{1c} only, and 26.2 (16.3–42.1) in those with both IFG and elevated HbA_{1c}.

Adding HbA_{1c} to FPG testing

The Spearman correlation coefficient between elevated HbA_{1c} and IFG was 0.31 ($P < 0.001$), allowing both variables to be included in the same model. Only participants with nonmissing values for all covariates were included in this analysis, resulting in a sample of 1,623, with 172 participants who developed diabetes during follow-up.

The AUC for the fully adjusted model with IFG was 0.76, and the AUC for the model additionally containing elevated HbA_{1c} was 0.83 (AUC difference 0.07, *P* value for AUC difference <0.001). The IDI for evaluation of the added predictive ability of the model with elevated HbA_{1c} was 0.10 (95% CI 0.08–0.12) with the relative IDI of 101.5% (*P* value <0.001). The NRI analysis with a prespecified risk category (<20 vs. ≥ 20% predicted risk for diabetes) resulted in 13.0% net reclassification improvement (95% CI 4.4–21.7%, $P = 0.004$) (Table 3). Net reclassification of 11.0% occurred in those with diabetes and 2.0% in those without diabetes. The Hosmer-Lemeshow χ^2 test showed *P* values that were not significant for both models, suggesting that the model fit was acceptable.

Sex and race differences

Diabetes developed in 83 (10.7%) of the men and 100 (11.0%) of the women ($P = 0.83$) and 102 (8.9%) of white and 81 (15.1%) of black participants ($P < 0.001$). The *P* values for interaction terms for sex and each of the three dummy-coded variables (IFG only, elevated HbA_{1c} only, and both) were 0.084, 0.016, and 0.002, respectively. Fully adjusted odds ratios for the development of diabetes in men were 8.6 (95% CI 3.4–21.9), 24.2 (9.5–61.8), and 51.1 (21.2–123.2) for IFG only, elevated HbA_{1c} only, and both IFG and elevated HbA_{1c}; in women, the corresponding odds ratios were 1.5 (0.5–4.6), 4.6 (2.4–8.7), and 20.4 (10.9–38.0), respectively.

The interaction terms for race and each of the three dummy-coded variables were not statistically significant. Fully adjusted odds ratios for the development of diabetes in white participants were 3.2 (95% CI 1.5–6.6), 10.2 (5.0–20.8), and 34.9 (19.1–63.8) for IFG only, elevated HbA_{1c} only, and both IFG and elevated HbA_{1c}; in black participants, the corresponding odds ratios were 4.6 (1.6–13.3), 5.8 (2.9–11.7), and 14.9 (6.8–32.6), respectively.

Sensitivity analyses

When we used diabetes definition based solely on *1*) self-report; *2*) self-report or use of diabetes medications only; *3*) self-report, use of diabetes medications, FPG ≥126 mg/dL, or HbA_{1c} ≥6.5%; or *4*) self-report, use of medications, or FPG ≥126 mg/dL, 95, 107, 199, and 141 individuals were identified as having incident diabetes, respectively. Logistic regression analyses using these definitions yielded qualitatively similar results to those of the primary analysis; however, IFG was a stronger predictor in models that used FPG-based outcomes. Results based on these definitions are shown in the Supplementary Data, with detailed results presented for the outcome based on self-report, use of medications, FPG, or HbA_{1c}. Cox proportional hazards regression based on the primary outcome (self-report, use of medications, or HbA_{1c} ≥6.5%) showed the following fully adjusted hazard ratios (HRs): 3.4 (95% CI 1.9–6.0), 7.6 (4.8–12.0), and 21.2 (14.0–32.3) for IFG only, elevated HbA_{1c} only, and both IFG and elevated HbA_{1c}, respectively. Fine and Gray analysis to account for competing risk of death yielded essentially the same HRs (Supplementary Data).

When we used the WHO definition of IFG (FPG 110 to <126 mg/dL), diabetes developed in 48% of those with the WHO definition of IFG (48 of 100). However, of 183 participants who developed diabetes, 135 did not have IFG according to WHO. The odds ratio for diabetes in the fully adjusted model was 11.4 (95% CI 7.1–18.4) in those with a WHO IFG (c index 0.72 [0.68–0.77]). When both WHO IFG and elevated HbA_{1c} were considered together, diabetes developed in 3.6% (46 of 1,279) of those with both normal tests, 34.3% (12 of 35) of those with WHO-defined IFG only, 28.6% (89 of 311) of those with elevated HbA_{1c} only, and 55.4% (36 of 65) of those with both abnormal tests.

CONCLUSIONS—In our longitudinal study, 10.8% of older adults developed diabetes over 7 years. We found that IFG and elevated HbA_{1c} increase the likelihood of developing diabetes over 7 years

Table 3—*Reclassification of predicted risk for diabetes after addition of HbA_{1c} to the model*

				Reclassified as increased risk (*n*)	Reclassified as decreased risk (*n*)	Correctly reclassified (%)**
Participants who developed diabetes* (*n* = 172)						
		Based on model with HbA_{1c}				
		<20% Predicted risk (*n*)	≥20% Predicted risk (*n*)			
Based on model without HbA_{1c}	<20% Predicted risk (*n*)	52	38	38	19	11.0
	≥20% Predicted risk (*n*)	19	63			
Participants who did not develop diabetes (*n* = 1,451)						
		Based on model with HbA_{1c}				
		<20% Predicted risk (*n*)	≥20% Predicted risk (*n*)			
Based on model without HbA_{1c}	<20% Predicted risk (*n*)	1,151	97	97	126	2.0
	≥20% Predicted risk (*n*)	126	77			
	Net reclassification improvement (95% CI)					13.0 (4.4, 21.7)***

*Diabetes defined by self-report, medications, or HbA_{1c}. **Percentage correctly reclassified for participants who developed diabetes is (38 − 19)/172 × 100 and for participants who did not develop diabetes (126 − 97)/1,451 × 100. ***$P = 0.004$.

by approximately 6- and 11-fold, respectively, compared with normal glycemic parameters. However, when FPG and HbA_{1c} results are considered together, the odds for diabetes in individuals with both abnormalities were substantially higher (~26-fold). Indeed, the ability to predict whether an older individual will develop diabetes was improved when the results of FPG and HbA_{1c} were considered together.

Several studies predominantly conducted in the middle-aged populations suggest that HbA_{1c} is strongly predictive of future diabetes (7–10). A recent systematic review involving a total of 44,203 individuals (mean age 53.4 years) showed that the 5-year incidence of diabetes ranged between 25 and 50% for baseline HbA_{1c} ≥6% and between 9 and 25% for baseline HbA_{1c} 5.5–6% across 16 studies (7). In addition, a recent examination of the value of HbA_{1c} in the Atherosclerosis Risk in Communities study (mean age 56.7 years) supports its strong association with subsequent diabetes, cardiovascular events, and mortality (23). One Japanese longitudinal study evaluated the value of HbA_{1c} in predicting diabetes and compared this directly with FPG (24). Among 6,241 adults without diabetes (mean age 49.9 years) and after a mean follow-up of 4.7 years, the adjusted risk for incident diabetes was increased similarly 6-fold for those with IFG alone and for those with elevated HbA_{1c} alone, but the risk was substantially higher (nearly 32-fold) for those identified by both IFG and elevated HbA_{1c} compared with normoglycemic individuals. However, these data are based on analysis of an ethnically homogeneous, predominantly male (75%), and younger cohort, which raises questions with regard to generalizability to older U.S.-based populations.

Few data on the actual incidence of new-onset diabetes in elderly individuals exist in the prior literature. In our study of older adults, 10.8% of participants developed diabetes over 7 years (roughly approximating an annual incidence of ~1.5% per year), which is similar to the annual incidence of diabetes among persons ≥65 years old in the U.S. (1.5% in 2011, according to the Centers for Disease Control estimates [25]). The effect of elevated HbA_{1c} and IFG on the odds of diabetes was comparable in our study with the effect observed in younger populations, although elevated HbA_{1c} appeared to be a stronger predictor in our study. Proportions of Health ABC participants who developed diabetes over 7 years were 10.6, 21.3, 47.9, and 3.4% in those with IFG alone, elevated HbA_{1c} alone, both IFG and elevated HbA_{1c}, and normal parameters at baseline, respectively (compared with the incidence of diabetes over 5 years of 8.5, 7.3, 37.6, and 1.1%, respectively, in the Japanese study) (mean age of 49.9 years [24]).

The ADA guidelines recommend the use of either test, HbA_{1c} or FPG, to identify individuals at risk for diabetes (1). Another option is to measure both tests, either simultaneously or in sequence, but this strategy is more costly (26). Several investigators have specifically evaluated whether obtaining two tests is better than either one alone in predominantly younger populations. In studies conducted in Japan and China, the ability to predict diabetes with both FPG and HbA_{1c} was significantly better than with either one alone (27–29). In a U.S. study, the incidence of diabetes was substantially increased in those with elevated FPG and HbA_{1c} compared with those with only one elevated test, but more detailed analyses of combined testing were not performed (8).

In the Health ABC study, over 7 years, diabetes developed in roughly one of four participants with IFG and one of three participants with elevated HbA_{1c}—when only one of these tests was considered. When both tests were considered together, the probability of diabetes was only 1–2 in 10 for participants with one elevated value (HbA_{1c} or FPG) and close to 1 in 2 for those with both elevated values. Interestingly, when the WHO definition of IFG was applied (FPG 110 to <126 mg/dL), participants with this type of IFG had a similar 1 in 2 probability of developing diabetes over time.

In our study, we also compared several measures of discrimination and calibration for models with and without elevated HbA_{1c}.The AUC, which reflects the ability to distinguish participants who develop diabetes from those who do not, improved significantly when elevated HbA_{1c} was added to the model already

containing IFG and several diabetes risk factors, although the absolute change was small (AUC difference 0.07, $P < 0.001$). Most new markers or risk do not result in a large absolute change in AUC, and some have questioned the utility of relying on AUC differences alone to establish the importance of new predictors (20). The relative value of IDI in our study indicates that the difference in predicted probabilities between events (diabetes) and nonevents (no diabetes) increased by 101.5% between the model without HbA_{1c} and the model with HbA_{1c}, resulting in a significantly greater discriminatory capacity. Perhaps the most intuitive and clinically relevant measure of model performance for diabetes prediction is the NRI. Using this method, we a priori selected two categories of risk that were clinically meaningful, indicating a predicted risk of diabetes of ≤20% during the follow-up period of our study. Thirteen percent of the participants were correctly reclassified for diabetes risk when HbA_{1c} was added to the model, which is a statistically significant difference ($P = 0.004$).

These data suggest that dual screening may improve identification of older participants with the highest odds of developing diabetes when the current definitions of prediabetes endorsed by the ADA are used. One could also argue for a stepwise approach, in which FPG is obtained first. If FPG is elevated by the WHO criterion (110 to <126 mg/dL), then the risk of diabetes is substantial (48% over 7 years according to our study), and further testing may not be necessary. If, on the other hand, FPG is normal by the ADA criterion (<100 mg/dL), diabetes risk is quite low at 6% over the next 7 years and, again, additional tests may not be required. When FPG is mildly elevated (i.e., 100–110 mg/dL), measuring HbA_{1c} may indeed help inform the patient and their care provider of subsequent diabetes risk. Although we did not evaluate the cost-effectiveness of dual testing strategies, our data do provide insight into interpretation of results of both HbA_{1c} and FPG—which are actually often available together in clinical practice.

It is worth noting that many prior studies on prediction of diabetes included only Caucasian subjects (9,10) or were confined to a single Asian group (24). It is now well recognized that the use of HbA_{1c} may differ depending on race, with consistently higher HbA_{1c} values obtained in black patients (3,16). These differences may reflect higher underlying glucose levels (30) or differences in the duration of hemoglobin exposure to glucose (31). In our biracial study, black individuals had a higher incidence of diabetes over time than white participants. The interaction between race, baseline glycemic status, and development of diabetes was not significant, suggesting that the overall results of our study can be applied to the black participant subgroup. We did find a significant interaction by sex: the odds ratio for diabetes associated with elevated HbA_{1c} or IFG was lower among women compared with men. Prior studies have not reported sex differences in prediction of diabetes based upon glycemic measures (8,32), and our results will need to be confirmed in future studies.

Our study should be considered in view of several limitations. Data on FPG and HbA_{1c} were not available at each annual follow-up, and therefore, logistic regression analyses were performed. Odds ratio can overestimate the risk ratio when the outcome of interest is common (>10%) (indeed, the 26.2-fold higher odds of diabetes in those with both elevated HbA_{1c} and IFG corresponds to a 14.1-fold higher risk ratio using the method of Zhang and Yu [33]). Our sensitivity analyses, which accounted for time-to-event, yielded qualitatively similar results. We defined the diagnosis of diabetes based on HbA_{1c} values, self-report, or medication use and did not apply a single FPG as a criterion. However, the results did not differ substantially when FPG was also considered in the outcome definition in a secondary analysis; however, in that analysis, IFG and elevated HbA_{1c} each increased the likelihood of diabetes similarly. Finally, we evaluated the impact of elevated HbA_{1c} and FPG on diabetes diagnosis but not on other outcomes that are important to patients. Effective interventions are available for adults diagnosed with prediabetes to reduce the risk of subsequent diabetes (based on glycemic measures) (34), but it is worth noting that there are no clear data on improvements in clinical outcomes, such as cardiovascular disease or microvascular complications. Future studies will need to evaluate whether screening for diabetes in this age-group with both FPG and HbA_{1c} leads to better health outcomes and whether this is cost-effective.

In summary, we found that IFG and elevated HbA_{1c} are associated with increased odds for subsequent diabetes in older adults. Obtaining both tests improves the ability to predict diabetes occurrence. Older adults with both IFG and elevated HbA_{1c} are at very high risk for diabetes, whereas those with two normal tests are unlikely to develop the disease over the next 7 years. Future studies of new-onset diabetes in older adults are needed to better understand the natural history of this condition and to document the effect of diabetes screening on clinical outcomes in the elderly.

Acknowledgments—This research was supported by National Institute on Aging (NIA) contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; NIA grant R01-AG028050; and National Institute of Nursing Research (NINR) grant R01-NR012459 and in part by the Intramural Research Program of the National Institutes of Health, NIA. K.J.L. was supported by NIA training grant T32AG1934 and is currently supported by the Pepper Center Career Development Award (P30 AG21342) and the Grants for Early Medical/Surgical Specialists' Transition to Aging Research (R03 AG045086) from the NIA. T.M.G. is the recipient of a Mid-career Investigator Award in Patient-Oriented Research (K24AG021507) from the NIA. The study was conducted at the Yale Claude D. Pepper Older Americans Independence Center (P30AG21342).

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

K.J.L. researched data, performed the statistical analysis, and wrote the manuscript. S.E.I. contributed to discussion and reviewed and edited the manuscript. P.H.V.N. contributed to discussion, reviewed and edited the manuscript, and contributed to statistical analysis. T.M.G. and A.Ka. contributed to discussion and reviewed and edited the manuscript. E.S.S. contributed to discussion, reviewed and edited the manuscript, and contributed to Health ABC study design. A.Ko., K.C.J., and B.H.G. contributed to discussion and reviewed and edited the manuscript. T.H. contributed to discussion, reviewed and edited the manuscript, and contributed to Health ABC study design. N.D.R. contributed to discussion, reviewed and edited the manuscript, and contributed to statistical analysis. K.J.L. 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.

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