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

Are two better than one?

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For the Health ABC Study

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.

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...
development of diabetes, and we evaluated the utility of combined testing for identifying older persons who develop diabetes. Since HbA1c 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 HbA1c 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, including 59 survivors who did not develop 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 HbA1c ≥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 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 HbA1c ≥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 HbA1c (5.7–6.4%). Participants were then categorized into four mutually exclusive groups: 1) normal glucose tolerance, based on FPG <100 mg/dL and HbA1c <5.7%; 2) IFG only, based on FPG 100–125 mg/dL but HbA1c <5.7%; 3) elevated HbA1c only, based on HbA1c 5.7–6.4% but FPG <100 mg/dL; and 4) both IFG and elevated HbA1c, based on FPG 100–125 mg/dL and HbA1c 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 HbA1c), and second, elevated HbA1c was compared with normal HbA1c (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 HbA1c, we developed a model with three dummy-coded variables: IFG only, elevated HbA1c only, and both IFG and elevated HbA1c (individuals who had neither IFG nor elevated HbA1c 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 (HbA1c and FPG) for predicting diabetes, we compared the fully adjusted model containing IFG with a model that additionally contained elevated HbA1c. 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 HbA1c)
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 rates 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 HbA1c compared with the model without elevated HbA1c. 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 $\chi^2$ 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 ($\geq$126 mg/dL), or HbA1c ($\geq$6.5%); and the fourth was based on self-report, use of medications, or FPG ($\geq$126 mg/dL). To address the timing of diabetes diagnosis, loss to follow-up, and death as a competing variable, we additionally analyzed the data using Cox proportional hazards regression and a Fine and Gray subdistribution hazards model (22) using the primary outcome of diabetes based on self-report, medication use, or HbA1c ($\geq$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 HbA1c 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 HbA1c, and 1,125 (66.6%) as having normal glucose tolerance (i.e., neither elevated FPG nor elevated HbA1c). Among participants with dysglycemia, 189 (33.5%) had IFG only, 207 (36.6%) had elevated HbA1c 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 HbA1c ($\geq$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 HbA1c) and elevated HbA1c (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 HbA1c, respectively. The c indices (for the two fully adjusted models with IFG and elevated

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

<table>
<thead>
<tr>
<th>Age (years), mean (SD)</th>
<th>76.5 (2.9)</th>
<th>76.4 (2.8)</th>
<th>76.6 (3.0)</th>
<th>76.7 (3.0)</th>
<th>76.6 (2.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% men)</td>
<td>46.1</td>
<td>42.8</td>
<td>66.7</td>
<td>39.6</td>
<td>52.7</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>68.2</td>
<td>72.9</td>
<td>82.0</td>
<td>36.2</td>
<td>60.4</td>
</tr>
<tr>
<td>Site (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>50.1</td>
<td>49.2</td>
<td>46.6</td>
<td>61.8</td>
<td>45.6</td>
</tr>
<tr>
<td>Memphis</td>
<td>49.9</td>
<td>50.8</td>
<td>53.4</td>
<td>38.2</td>
<td>54.4</td>
</tr>
<tr>
<td>SBP (mmHg), mean (SD)</td>
<td>140.3 (21.2)</td>
<td>139.8 (20.9)</td>
<td>142.6 (23.1)</td>
<td>141.8 (21.4)</td>
<td>139.5 (20.6)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>27.0 (4.7)</td>
<td>26.4 (4.5)</td>
<td>27.9 (4.5)</td>
<td>27.9 (5.4)</td>
<td>29.0 (4.9)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>7.1</td>
<td>7.6</td>
<td>4.4</td>
<td>7.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Former</td>
<td>45.9</td>
<td>42.9</td>
<td>52.2</td>
<td>46.5</td>
<td>58.2</td>
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<tr>
<td>Walking time (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43.4</td>
<td>41.2</td>
<td>46.3</td>
<td>50.7</td>
<td>46.4</td>
</tr>
<tr>
<td>&lt;150 min/week</td>
<td>35.0</td>
<td>36.1</td>
<td>31.9</td>
<td>33.3</td>
<td>33.3</td>
</tr>
<tr>
<td>≥150 min/week</td>
<td>21.5</td>
<td>22.7</td>
<td>21.8</td>
<td>15.9</td>
<td>20.2</td>
</tr>
<tr>
<td>FPG (mg/dL), mean (SD)</td>
<td>92.8 (9.5)</td>
<td>88.4 (6.2)</td>
<td>105.3 (4.9)</td>
<td>92.3 (5.2)</td>
<td>108.7 (6.0)</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>5.3 (0.4)</td>
<td>5.2 (0.3)</td>
<td>5.3 (0.3)</td>
<td>5.8 (0.2)</td>
<td>5.9 (0.2)</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; BMI, body mass index; SBP, systolic blood pressure.
HbA1c 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 34.9% of those with normal FPG and HbA1c, 34.3% (12 of 35) of those with both abnormal FPG and elevated HbA1c, 24.2 (9.5–13.3%) of black participants (c index 0.72 [0.68–0.77]). When both WHO IFG and elevated HbA1c 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 both elevated HbA1c only, and 55.4% (36 of 65) of those with both abnormal tests.

**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 HbA1c 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 HbA1c only, and both IFG and elevated HbA1c; 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 all 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 HbA1c only, and both IFG and elevated HbA1c; 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 HbA1c ≥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 HbA1c. Cox proportional hazards regression based on the primary outcome (self-report, use of medications, or HbA1c ≥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 HbA1c only, and both IFG and elevated HbA1c, 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 HbA1c 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 both elevated HbA1c 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 HbA1c increase the likelihood of developing diabetes over 7 years.
Table 3—Reclassification of predicted risk for diabetes after addition of HbA1c to the model

<table>
<thead>
<tr>
<th>Participants who developed diabetes* (n = 172)</th>
<th>Reclassified as increased risk (n)</th>
<th>Reclassified as decreased risk (n)</th>
<th>Correctly reclassified (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on model with HbA1c</td>
<td>&lt;20% Predicted risk (n)</td>
<td>≥20% Predicted risk (n)</td>
<td></td>
</tr>
<tr>
<td>Based on model without HbA1c</td>
<td>&lt;20% Predicted risk (n)</td>
<td>≥20% Predicted Risk (n)</td>
<td></td>
</tr>
<tr>
<td>Participants who did not develop diabetes (n = 1,451)</td>
<td>1,151</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Based on model with HbA1c</td>
<td>&lt;20% Predicted risk (n)</td>
<td>≥20% Predicted risk (n)</td>
<td></td>
</tr>
<tr>
<td>Based on model without HbA1c</td>
<td>&lt;20% Predicted risk (n)</td>
<td>≥20% Predicted Risk (n)</td>
<td></td>
</tr>
</tbody>
</table>

Net reclassification improvement (95% CI): 13.0 (4.4, 21.7)**

*Diabetes defined by self-report, medications, or HbA1c. **Percentage correctly reclassified for participants who developed diabetes is (38-19)/172 * 100 and for participants who did not develop diabetes (126-97)/1451 * 100. ***p = 0.004.

by approximately 6– and 11-fold, respectively, compared with normal glycemic parameters. However, when FPG and HbA1c 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 HbA1c were considered together.

Several studies predominantly conducted in the middle-aged populations suggest that HbA1c 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 HbA1c ≥6% and between 9 and 25% for baseline HbA1c 5.5–6% across 16 studies (7). In addition, a recent examination of the value of HbA1c 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 HbA1c 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 HbA1c alone, but the risk was substantially higher (nearly 32-fold) for those identified by both IFG and elevated HbA1c 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 (though 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 HbA1c and IFG on the odds of diabetes was comparable in our study with the effect observed in younger populations, although elevated HbA1c 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 HbA1c alone, both IFG and elevated HbA1c, 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, HbA1c 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 HbA1c 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 HbA1c 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 HbA1c—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 (HbA1c 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 HbA1c. The AUC, which reflects the ability to distinguish participants who develop diabetes from those who do not, improved significantly when elevated HbA1c was added to the model already...
Predicting diabetes incidence in older adults

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 Hba1c and the model with Hba1c, 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 \( \leq 20\% \) during the follow-up period of our study. Thirteen percent of the participants were correctly reclassified for diabetes risk when Hba1c 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 \(< 126 \text{ mg/dL} \)), 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 (\(< 100 \text{ mg/dL} \)), 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 Hba1c 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 Hba1c 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 Hba1c may differ depending on race, with consistently higher Hba1c 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 Hba1c 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 Hba1c 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 Hba1c 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 Hba1c 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 Hba1c each increased the likelihood of diabetes similarly. Finally, we evaluated the impact of elevated Hba1c 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 Hba1c leads to better health outcomes and whether this is cost-effective.

In summary, we found that IFG and elevated Hba1c 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 Hba1c 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.

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