Simultaneous Consideration of HbA_{1c} and Insulin Resistance Improves Risk Assessment in White Individuals at Increased Risk for Future Type 2 Diabetes

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Type 2 diabetes (T2D) prevalence increases unabated even as interventions focused on individuals at high risk can prevent T2D (1). Best approaches to identify individuals at high risk continue to be refined. Current risk assessment focuses on elevated glycemia, commonly estimated by fasting glucose (FG) and HbA_{1c} levels, despite imperfect sensitivity and specificity (2). We previously showed that risk for T2D increases progressively as HbA_{1c} increases, independently and in addition to increasing FG (3,4). As risk assessment for T2D depends on more than glycemia alone, simultaneous consideration of another physiological axis may improve biomarker-based diagnostic precision. Here, we test the hypothesis that simultaneous consideration of HbA_{1c} and insulin resistance (IR), assessed with fasting insulin as HOMA of IR (HOMA-IR), can substantially improve risk assessment for T2D.

We have previously detailed our statistical approach, IR and T2D diagnostic criteria, and particulars of the Framingham Heart Study (FHS) (3). Using the same FHS data and excluding those with T2D at baseline, we categorized individuals according to HbA_{1c} <5.7% or 5.7–6.49% and into HOMA-IR tertiles and followed them for a mean (SD) of 16.4 (4.5) years for incident T2D.

Age- and sex-adjusted T2D incidence rates and counts of subjects are shown in Fig. 1*A* for all 2,205 study subjects and 1,583 normoglycemic subjects with FG <100 mg/dL. Incidence was high in those with HbA_{1c} 5.7–6.49% and HOMA-IR in the top two tertiles, or with HbA_{1c} <5.7% and HOMA-IR in the top tertile, relative to those in lower categories. Age- and sex-adjusted models for those with HbA_{1c} 5.7–6.49% compared with those with HbA_{1c} <5.7% and for HOMA-IR tertile 3 versus tertile 2 or 1 are shown in Fig. 1*B*. Elevated HbA_{1c} and HOMA-IR independently predicted T2D in all and in normoglycemic subjects. The association between HbA_{1c} and risk of T2D did not differ according to HOMA-IR tertile (all first-order interactions $P > 0.1$). Area under the receiver operating characteristic curves (AUC) and continuous net reclassification indices are shown in Fig. 1*C*. Addition of HOMA-IR to age- and sex-adjusted HbA_{1c} prediction models in all subjects, and even in normoglycemic subjects, significantly improved correct classification of T2D risk.

Strengths of this study include testing of a relevant clinical question using a well-validated approach in a well-known cohort. Limitations include study of white individuals only and small numbers of T2D events in some subgroups. Also, a more precise surrogate marker of IR than HOMA-IR would identify a greater proportion of individuals at high risk, but most measures require at least an oral glucose tolerance test. For instance, fasting insulin and C-peptide measured with mass spectrometry afford an alternate simple approach to classify IR (5).

HbA_{1c} and fasting insulin are both commonly available clinical diagnostic tests. Consideration of both tests combined identifies highly increased risk for future T2D in the great majority of white individuals, even those with apparently normal HbA_{1c}.

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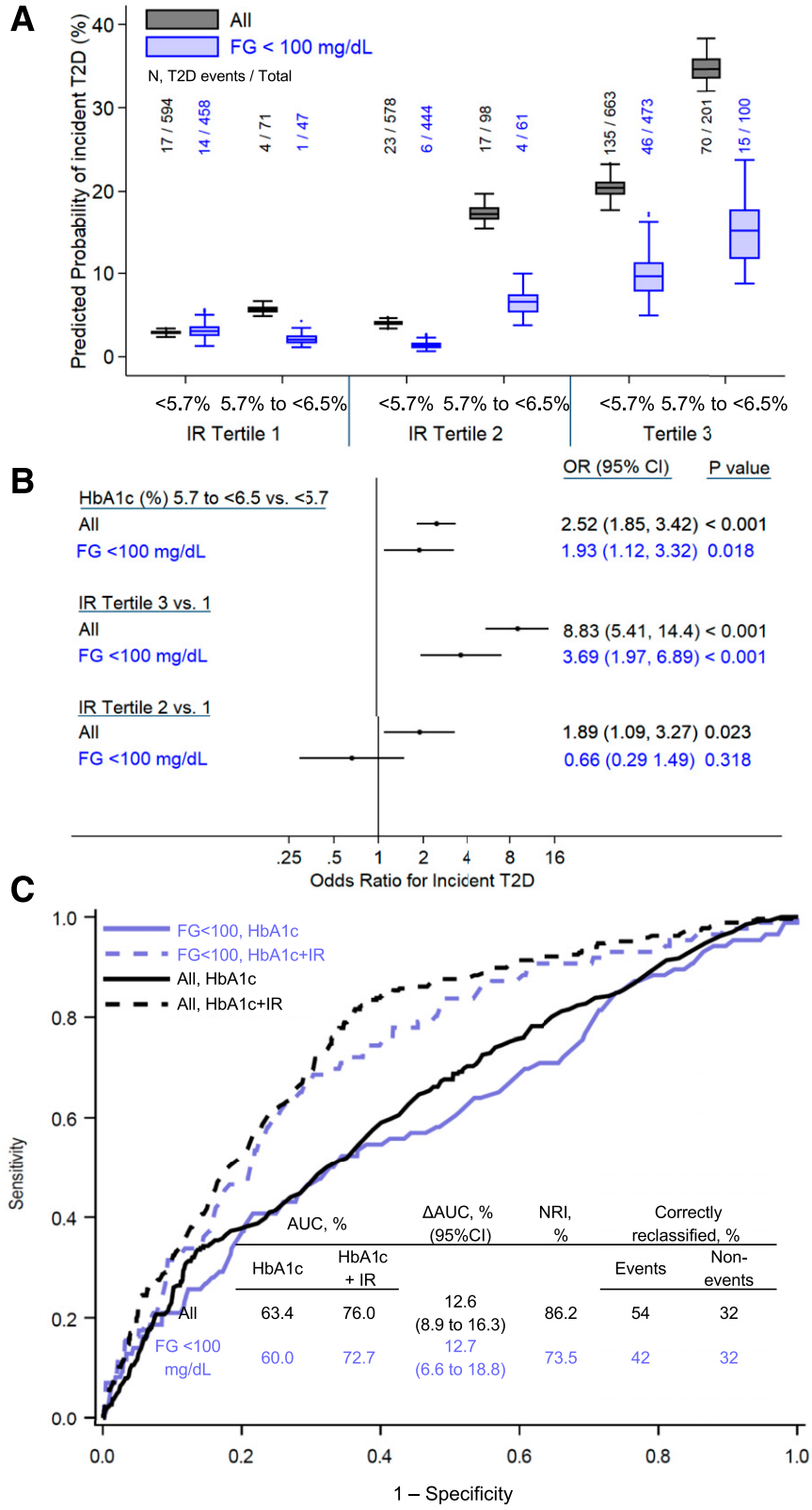

Figure 1—*A*: Risk for incident T2D increases with increasing HbA_{1c} and HOMA-IR category. The graph shows the predicted probability of incident T2D (*y*-axis), by tertiles of HOMA-IR stratified by HbA_{1c} <5.7% or 5.7% to <6.5% (*x*-axis), for all study subjects (black data series) and among those with FG <100 mg/dL (blue data series). The inset numbers indicate the number of T2D events/the total sample size in each category group for all study subjects (black font) and among those with FG <100 mg/dL (blue font). The box plots represent the first quartile (lower hinge), median, and third quartile (upper hinge) of the risk distribution, and the whiskers indicate 1.5 times the interquartile range. *B*: Elevated HbA_{1c} and HOMA-IR are independent risk factors for incident T2D. The graph shows odds ratios, 95% CIs, and *P* values for terms for HbA_{1c} <5.7% vs. 5.7% to <6.5%, HOMA-IR tertile 3 vs. tertile 1, and HOMA-IR tertile 2 vs. tertile 1 from a model containing age, sex, HbA_{1c} category, and HOMA-IR category, for models of all study subjects (black data

plan; compiled results; and drafted the manuscript. B.P. and J.B.M. contributed to the scientific hypothesis, study design, and analysis plan. B.P. and A.L. performed analyses and prepared the figure. J.B.M., B.P., A.L., D.S., J.J.D., and M.J.M. reviewed all aspects of the manuscript and approved of 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.

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series) and among those with FG $<$100 mg/dL (blue data series). *C*: HOMA-IR improves discrimination and reclassification when added to HbA_{1c} in prediction models. The graph shows AUC, with sensitivity on the *y*-axis and 1 − specificity on the *x*-axis, for age- and sex-adjusted regression models predicting incident T2D that include categorical HbA_{1c} (solid lines) or HbA_{1c} plus HOMA-IR (dashed lines), for all study subjects (black data series) and among those with FG $<$100 mg/dL (blue data series). The inset shows the value of AUC for the HbA_{1c} and HbA_{1c} plus HOMA-IR models, the difference [ΔAUC (95% CI)] between those AUCs, the continuous net reclassification indices, and the proportion of T2D events and nonevents correctly reclassified with addition of HOMA-IR to HbA_{1c} prediction models for all study subjects (black font) and among those with FG $<$100 mg/dL (blue font).