An Insulin Resistance Score Improved Diabetes Risk Assessment in the Malmö Prevention Project—A Longitudinal Population-Based Study of Older Europeans

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The worldwide prevalence of type 2 diabetes (T2D) continues to increase, despite the established efficacy of T2D prevention interventions. Identifying individuals at high risk and making them the focus of preventive interventions may reduce the incidence of diabetes and global disease burden. We recently showed that T2D risk assessment in white middle-aged men and women can be improved with addition of an insulin resistance measure (assessed by HOMA of insulin resistance) to glycemia and other established risk factors (1). We have also developed an insulin resistance score (IRScore), comprising fasting insulin and C-peptide measured by mass spectrometry, to assess the probability of existing insulin resistance where insulin resistance was defined as being in the top tertile of steady-state plasma glucose level (≥198 mg/dL) (2).

In the current study, we asked whether this IRScore improved T2D risk assessment beyond glycemia and established risk factors in a population of older Europeans. Older populations are of particular interest given the steady increase in the average age worldwide, especially in Europe, Japan, China, and the U.S. We conducted a case-cohort study based on the Malmö Prevention Project, a longitudinal population-based study of 18,240 residents of southern Sweden whose baseline assessment and bio-sample collection took place between 2002 and 2006 (3). A randomly selected cohort sample (3) comprised 4,093 individuals (323 incident T2D events) after exclusion of participants with diabetes at baseline (fasting glucose >125 mg/dL) or with missing data. The study was supplemented with all incident events outside the cohort sample (n = 772 patients for a total of 1,095 incident events) and thus included 4,865 participants (32% of whom were women; median age 68 years [interquartile range 66–73]). Incident T2D was assessed in December 2014 (median follow-up time 9.1 years) with linking of a 10-digit personal identification number of each Swedish citizen to Swedish disease registries (4). The study was approved by the regional ethics review board in Lund, Sweden, and complies with the Declaration of Helsinki. We assessed the association of the IRScore with incident T2D using a Cox proportional hazards regression model with adjustment for the following established risk factors measured at baseline: age, sex, BMI, waist circumference, parental history of diabetes, hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or being on antihypertensive medications), HDL cholesterol, and triglycerides and, in a second model, these plus prediabetes status (fasting glucose below vs. greater than or equal to 100 mg/dL).

Being in the top versus the bottom tertile of IRScore was associated with incident T2D (Fig. 1) (hazard ratio [HR] 2.1, 95% CI 1.7–2.5, $P < 0.0001$) after adjustment for all established risk factors except for prediabetes status. Addition of prediabetes to the model attenuated the association (HR 1.5, 95% CI 1.3–1.8, $P < 0.0001$). As expected, prediabetes was associated with incident diabetes (HR 3.9, 95% CI 3.4–4.5, $P < 0.0001$). We next assessed the improvement in 5-year T2D risk prediction using continuous net reclassification index. The addition of IRScore to a model that included established risk factors (including prediabetes) resulted in net reclassification index of 42% (95% CI 34–50). Among those without incident T2D, 21% (95% CI 18–24) were reclassified as at lower risk. And among those with incident T2D, 21% (95% CI 13–29) were reclassified as at higher risk. The area under the receiver operating characteristic curve improved from 0.77 for the established risk factors model (including prediabetes) to 0.78 for a model that also included the IRScore ($P < 0.001$).

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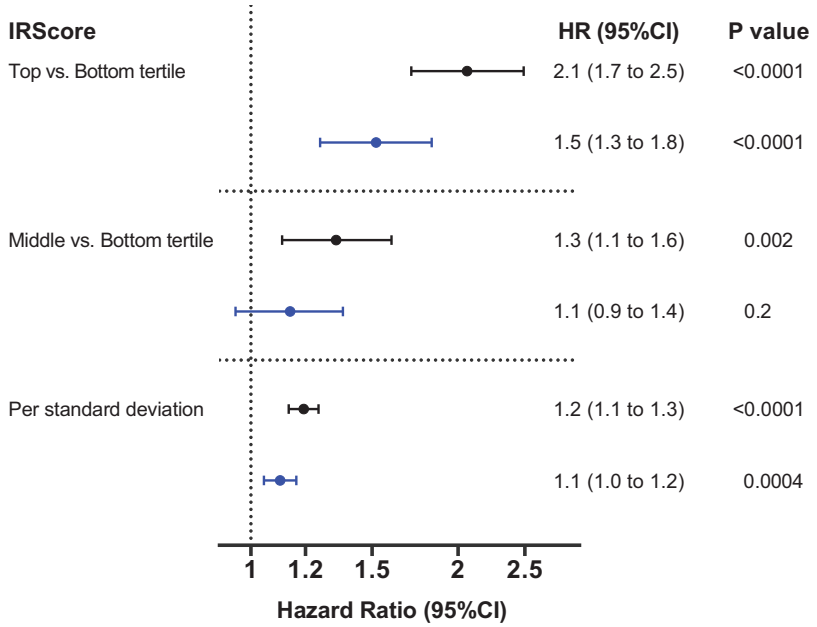

- Model 1: adjusted for age, sex, body-mass index, waist circumference, parental history of diabetes, hypertension, HDL-C, and triglycerides
- Model 1 adjustments + prediabetes status

IRScore cut points
Top tertile, >3.137 (>20% insulin resistance probability)
Bottom tertile: <1.924 (<7% insulin resistance probability)

	IRScore Tertile			
Event status	**Bottom**	**Middle**	**Top**	**Total**
No events (n)	1420	1295	1055	3770
T2D event (n)	201	326	568	1095
Total	1621	1621	1623	4865

Figure 1—The IRScore is associated with incident type 2 diabetes.

The study generalizability is limited by the European ancestry of almost all study participants. However, the large number of events in the study increases its internal validity and helps confirm that older individuals with insulin resistance have elevated risk of T2D. We conclude that the IRScore is associated with T2D regardless of prediabetes status (i.e., with fasting glucose level above or below 100 mg/dL). In other words, the IRScore identified individuals at high risk who would not have been considered to be at high risk based on glucose testing combined with other established risk factors. Given the unabated diabetes epidemic, serious consideration should be given regarding improvement of screening and diagnostic strategies to focus interventions on the individuals at highest risk. Measurement of glucose and insulin resistance may reflect just two of the "ominous octet" (5), but combining them to assess diabetes risk takes advantage of the hetero-geneous diabetes phenotype to improve precision of risk assessment.

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