Natural History of Prediabetes and Long-term Risk of Clinical Outcomes in Middle-aged Adults: The Atherosclerosis Risk in Communities (ARIC) Study

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Clinical guidelines recommend screening for prediabetes in asymptomatic adults ≤70 years of age (1,2). Three laboratory measurements are used for screening: HbA_{1c}, fasting glucose (FG), and 2-h postload glucose. American Diabetes Association guidelines require two positive tests, either two different tests or repeated measures of the same test, to diagnose diabetes. However, only one positive test is recommended to diagnose prediabetes (2), resulting in a large and heterogenous population with prediabetes (3). It is unclear if a two-test approach could improve the specificity of prediabetes definitions in the general population. To better quantify prognosis in different definitions of prediabetes, we characterized patterns of progression from prediabetes to diabetes or remission to normoglycemia in the community-based Atherosclerosis Risk in Communities (ARIC) study. We also examined subsequent long-term morbidity and mortality associated with patterns of progression or remission.

We conducted an analysis of 7,926 adults without diabetes (aged 48–68 years) from the ARIC study visit 2 (V2) (1990–1992) and visit 4 (V4) (1996–1998). Participants were classified by impaired FG (IFG) 100–125 mg/dL and HbA_{1c} 5.7–6.4% at V2. We calculated 6-year risk of progression to diabetes and regression to normoglycemia (FG <100 mg/dL and 2-h postload glucose <140 mg/dL).

For long-term outcomes, participants were classified by the V2 categories of HbA_{1c} and FG and also by change in FG (the only glycemic marker available at both visits): 1) stable normal FG (NFG) (<100 mg/dL at both visits), 2) progression to IFG (<100 mg/dL at V2 but 100–125 mg/dL at V4), 3) remission of IFG (100–125 mg/dL at V2 but <100 mg/dL at V4), and 4) persistent IFG (100–125 mg/dL at both visits).

Participants were followed through 2019 (maximum 29.9 years) for incident diabetes, heart failure (HF), atherosclerotic cardiovascular disease (ASCVD), and mortality. Participants were followed through 2017 for kidney failure (KF) (permanent dialysis, kidney transplantation, or estimated glomerular filtration rate <15 mL/min/1.73 m²) from the U.S. Renal Data System. Incident diabetes was defined as self-report of physician-diagnosed diabetes or use of glucose-lowering medications during any follow-up visit or annual phone call.

Of 7,926 participants at V2, 57% had normoglycemia, 27% had isolated elevated FG, 6% had isolated elevated HbA_{1c}, and 10% had elevations on both tests. Compared with normoglycemia, participants with elevations in both FG and HbA_{1c} at V2 had the highest risk of long-term outcomes: hazard ratio (HR) 5.87 (95% CI 5.30–6.52) for diagnosed diabetes, 2.25 (95% CI 1.78–2.85) for

KF, 1.75 (95% CI 1.54–1.98) for HF, 1.87 (95% CI 1.65–2.11) for ASCVD, and 1.46 (95% CI 1.34–1.58) for mortality.

The 6-year risk of diabetes was 3.5% in participants with isolated IFG, 4.9% with isolated elevated HbA_{1c}, and 15.2% with elevations in both. BMI was strongly associated with diabetes, particularly in people with IFG and elevated HbA_{1c} (Fig. 1).

When evaluating progression of FG (V2 to V4), most (55%) had stable NFG, 20% had persistent IFG, 10% progressed from NFG to IFG, and 15% experienced remission of IFG. Compared with stable NFG, participants with remission of IFG had no increased risk of mortality (HR 1.02, 95% CI 0.92–1.14), KF (HR 0.81, 95% CI 0.54–1.22), HF (HR 1.02, 95% CI 0.86–1.22), or ASCVD (HR 1.06, 95% CI 0.89–1.26), but they did have higher risk of progressing to diagnosed diabetes (HR 1.99, 95% CI 1.72–2.31). Participants with persistent IFG had increased risk of mortality (HR 1.18, 95% CI 1.07–1.30), KF (HR 1.49, 95% CI 1.10–2.01), HF (HR 1.39, 95% CI 1.20–1.61), ASCVD (HR 1.29, 95% CI 1.10–1.50), and incident diabetes (HR 4.18, 94% CI 3.71–4.71).

A confirmatory definition of prediabetes (elevations in both FG and HbA_{1c}) identified individuals most likely to develop diabetes and long-term clinical outcomes. A substantial portion of our study population with prediabetic FG had normal FG at the 6-year follow-up

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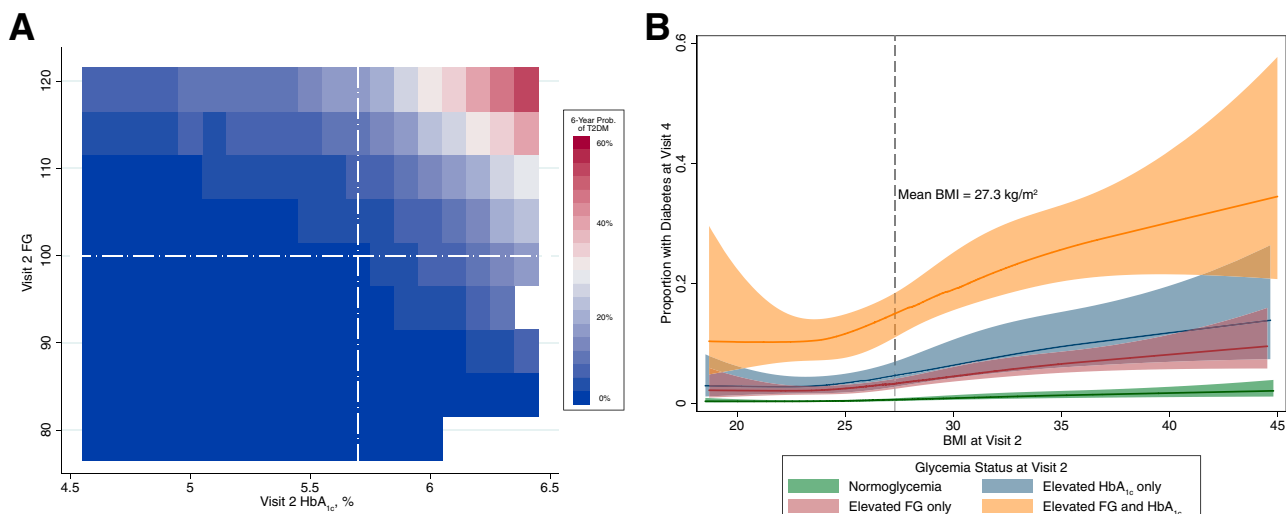[3]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University, Baltimore, MD
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Figure 1—Adjusted 6-year probability of progression to diabetes by FG and HbA$_{1c}$ (*A*) and glycemic status and BMI (*B*) from ARIC V2 (1990–1992) to V4 (1996–1998). Results were adjusted for age, sex, and race. Dashed lines represent cutoffs for prediabetes categories. T2DM, type 2 diabetes mellitus.

visit, and they did not have increased risk of most long-term outcomes.

Current definitions of prediabetes identify approximately one-third of the population (88 million U.S. adults in 2018) (4) as eligible for lifestyle interventions like the Diabetes Prevention Program. These programs have been shown to be cost-effective at preventing or delaying the development of diabetes and its complications (5), and they are being implemented nationally in the U.S. Given the number of people eligible for diabetes prevention programs, risk stratification may be useful for programs with limited resources. Our results suggest that using a confirmatory (two-test) definition of prediabetes (both elevated HbA$_{1c}$ and FG) identified individuals at highest risk for developing diabetes; the addition of BMI further improved risk stratification. A single elevated FG in middle-aged adults was common, tended to resolve, and was not highly prognostic of future disease. Requiring two elevations in measures of

glycemia to define prediabetes improves risk stratification for future diabetes and major clinical outcomes.

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