Lifetime Prevalence and Prognosis of Prediabetes Without Progression to Diabetes

Diabetes Care 2018;41:e117–e118 | https://doi.org/10.2337/dc18-0524

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Impaired fasting glucose, also termed prediabetes, is increasingly prevalent and is associated with adverse cardiovascular risk (1). The cardiovascular risks attributed to prediabetes may be driven primarily by the conversion from prediabetes to overt diabetes (2). Given limited data on outcomes among nonconverters in the community, the extent to which some individuals with prediabetes never go on to develop diabetes and yet still experience adverse cardiovascular risk remains unclear. We therefore investigated the frequency of cardiovascular versus noncardiovascular deaths in people who developed early- and late-onset prediabetes without ever progressing to diabetes.

We used data from the Framingham Heart Study collected on the Offspring Cohort participants aged 18–77 years at the time of initial fasting plasma glucose (FPG) assessment (1983–1987) who had serial FPG testing over subsequent examinations with continuous surveillance for outcomes including cause-specific mortality (3). As applied in prior epidemiological investigations (4), we used a case-control design focusing on the cause-specific outcome of cardiovascular death to minimize the competing risk issues that would be encountered in time-to-event analyses. To focus on outcomes associated with a given chronic glycemic state maintained over the entire lifetime, we restricted our analyses to only those participants for whom data were available over the life course and until death. We included participants who attended seven serial examinations until the end of life, with cause of death adjudicated as cardiovascular versus noncardiovascular (through 31 December 2014) (3). We excluded individuals with unknown age of onset of glycemic impairment (i.e., age $\geq$50 years with prediabetes or diabetes at enrollment). We defined diabetes as FPG $\geq$126 mg/dL or glucose-lowering medication use and prediabetes as FPG 100–125 mg/dL (5). We defined the presence of prediabetes or diabetes as meeting the above criteria at $\geq$2 consecutive examinations (to ensure stability of glycemic phenotypes over time), and early onset as meeting criteria at age $<$50 years.

We analyzed cause-specific mortality, allowing for relating time-varying exposures with lifetime risk for an event (4). We related glycemic phenotypes to cardiovascular versus noncardiovascular cause of death using a case-control design, where cases were defined as individuals who died of cardiovascular disease (death from stroke, heart failure, or other vascular event) or coronary heart disease (CHD) and controls were those who died of other causes. We used logistic regression to examine the risk of death from cardiovascular disease or CHD versus death from other causes across the following glycemic phenotypes: *1*) never diabetes or prediabetes, *2*) early-onset prediabetes and never diabetes, *3*) late-onset prediabetes and never diabetes, and *4*) ever diabetes. We adjusted for age at death, sex, and other covariates (smoking status, total cholesterol, hypertension, and BMI) assessed at the last available examination. We fit LOESS-smoothed curves for mean FPG values observed at ages 30–70 years to illustrate longitudinal FPG tracking in each glycemic phenotype.

The mean age of participants at enrollment was 42 $\pm$ 7 years (43% women). The mean age at death was 73 $\pm$ 10 years. Fig. 1*A* shows the mean FPG by age for each glycemic phenotype. In our overall sample (including cases and controls), the lifetime prevalence of dysglycemia (prediabetes or diabetes) was 50% (n = 602), of which the prevalence of individuals who developed prediabetes but never progressed to diabetes was 69% (n =

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Received 9 March 2018 and accepted 7 April 2018.

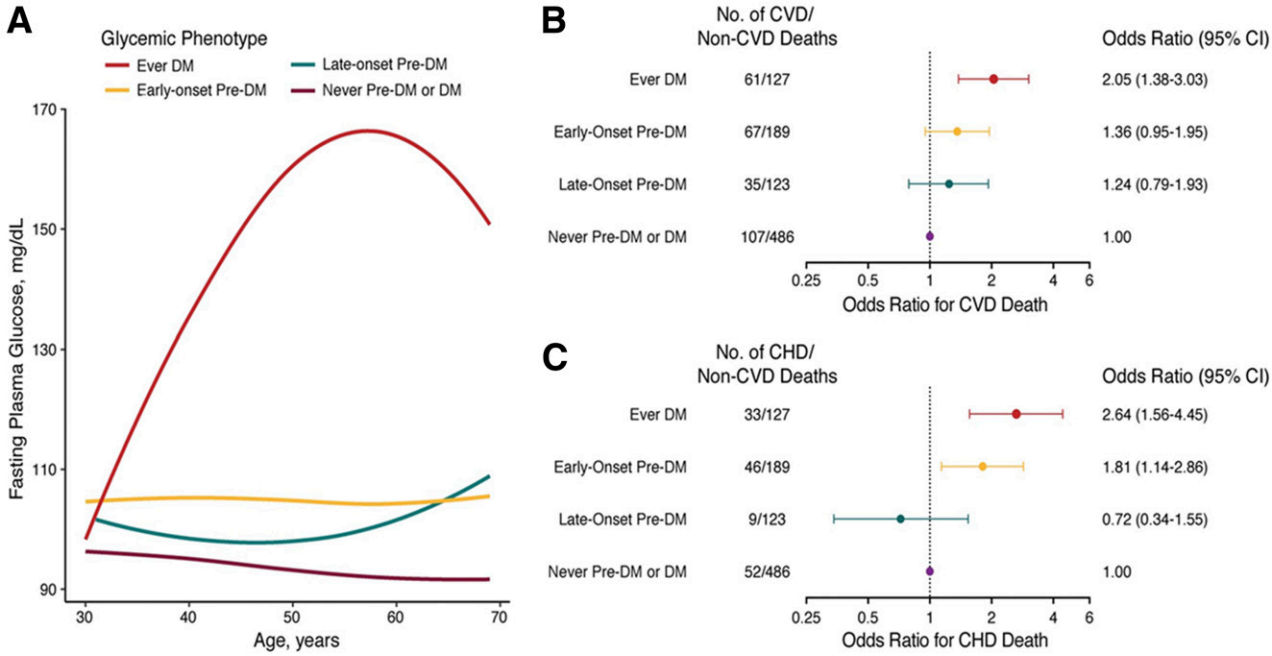

Figure 1—*A*: Mean FPG with increasing age by glycemic phenotype, including individuals with treated diabetes (red line). *B* and *C*: Odds of cardiovascular and coronary death vs. noncardiovascular death by glycemic phenotype. Age at death, sex, smoking status, serum total cholesterol, cohort, and hypertension are included as covariates in the models. CVD, cardiovascular disease; DM, diabetes.

414). In comparisons to controls, the risks of cardiovascular death (Fig. 1*B*) and of CHD-related death (Fig. 1*C*) increased across the spectrum of lifetime glycemic phenotypes. When compared with individuals who maintained optimal FPG throughout life, having ever developed diabetes was associated with considerably increased odds of cardiovascular and coronary death versus death from other causes. With respect to prediabetes without progression to diabetes, earlier-onset rather than later-onset prediabetes was associated with significantly increased odds of coronary death (Fig. 1*C*) but nonsignificantly with higher odds of cardiovascular death (Fig. 1*B*).

In our study, approximately half of the individuals presented with glycemic impairment in their lifetime, of whom two-thirds developed prediabetes but never diabetes. In our study, these individuals had lower cardiovascular-related mortality compared with those who later developed diabetes, even if the prediabetes onset was early in life. However, individuals with early-onset prediabetes, despite lifelong avoidance of overt diabetes, had greater propensity for death due to cardiovascular or coronary versus noncardiovascular disease compared with those who maintained lifelong normal glucose status.

Prediabetes is a heterogeneous entity. Whereas some forms of prediabetes are precursors to diabetes, other types of prediabetes never progress to diabetes but still confer increased propensity for death from a cardiovascular cause. Our findings, indicating greater risk with earlier-onset compared with later-onset prediabetes, suggest that further investigations are needed to determine whether interventions that can delay the age of prediabetes onset may, in turn, reduce the overall burden of cardiovascular disease (2).

Acknowledgments. The authors are grateful to the participants of the Framingham Heart Study for invaluable contributions to this work.
Funding. This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contract no. N01-HC-25195) and HHSN268201500001I (R.S.V.) and by the following grants: T32-HL-125232 (J.B.E.-T.), R01-HL-093328 (R.S.V.), R01-HL-107385 (R.S.V.), R01-HL-126136 (R.S.V.), R00-HL-107642 (S.C.), R01-HL-131532 (S.C.), and R01-HL-134168 (M.J., S.C.).
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. J.B.E.-T., T.J.N., M.J., and S.C. conceived and designed the study. J.B.E.-T., T.J.N., E.L.M., M.J., R.S.V., M.G.L., and S.C. analyzed and interpreted the data. J.B.E.-T. and S.C. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. J.B.E.-T., R.S.V., M.G.L., and S.C. approved the final manuscript. E.L.M. and M.G.L. provided statistical expertise. R.S.V. and S.C. obtained funding. S.C. provided administrative, technical, or logistic support. J.B.E.-T. is the guarantor of this work and, as such, had full access to all of 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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