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Comparative Prognostic Performance of Definitions of Prediabetes in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—There is a lack of consensus across international organizations regarding definitions of prediabetes. Associations with complications can inform the comparative value of different prediabetes definitions.

Methods—We conducted a prospective cohort study of 10,844 Atherosclerosis Risk in Communities (ARIC) study participants without diagnosed diabetes who attended visit 2 (1990–92) and 7,194 who attended visit 4 (1996–98). Fasting glucose and HbA1c were measured at visit 2 and fasting glucose and 2-hour glucose were measured at visit 4. We compared prediabetes definitions based on fasting glucose (American Diabetes Association [ADA] 5.6–6.9 mmol/L and

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World Health Organization [WHO] 6.1–6.9 mmol/L), HbA1c (ADA 39–46 mmol/mol and International Expert Committee [IEC] 42–46 mmol/mol), and 2-hour glucose (ADA/WHO 7.8–11.0 mmol/L).

Findings—ADA fasting glucose-defined prediabetes (prevalence 37.9%) was the most sensitive for major clinical outcomes, while ADA and IEC HbA1c and WHO fasting glucose-based definitions (prevalence 18.7%, 9.0%, 11.2%, respectively) were more specific. After demographic adjustment, HbA1c-based definitions of prediabetes had higher hazard ratios and demonstrated better risk discrimination for chronic kidney disease, cardiovascular disease, peripheral arterial disease, and all-cause mortality compared to fasting glucose (modestly larger C-statistics, all $p<0.05$). For example, the C-statistic for incident chronic kidney disease was 0.636 for ADA fasting glucose categories and 0.640 for ADA HbA1c clinical categories (difference −0.005, 95%CI −0.008, −0.001). Additionally, ADA HbA1c-defined prediabetes also demonstrated significant overall improvement in the net reclassification index for cardiovascular outcomes and death compared to glucose-based definitions. Comparing ADA and WHO fasting glucose and ADA/WHO 2-hour did not reveal statistically significant differences in risk discrimination for chronic kidney disease, cardiovascular, or mortality outcomes.

Interpretation—Our results suggest that HbA1c-defined prediabetes definitions were more specific and provided modest improvements in risk discrimination for clinical complications. ADA fasting glucose was a more sensitive definition overall.

Prediabetes is a pressing clinical and public health problem, which affects approximately 12% to 30% of U.S. adults age 18 years and older, depending on the definition used. (1) International organizations largely agree on the clinical cut-points for diagnosis of diabetes and, in 2010, HbA1c ≥ 48 mmol/mol was adopted for diagnosis of diabetes by many international groups, in part based on the association of HbA1c with retinopathy (2–5). By contrast, the category of prediabetes does not have a uniform definition. The American Diabetes Association (ADA) recommends identifying persons with prediabetes using the following definitions: fasting glucose between 5.6–6.9 mmol/L (100–125 mg/dL; “impaired fasting glucose”), HbA1c between 39–46 mmol/mol (5.7–6.4%), or 2-hour glucose following a 75–g oral glucose tolerance test between 7.8–11.0 mmol/L (140–199 mg/dL; “impaired glucose tolerance”) (6). The World Health Organization (WHO) also recommends 2-hour glucose 7.8–11.0 mmol/L, but recommends a fasting glucose of 6.1–6.9 mmol/L (110–125 mg/dL) to identify “impaired fasting glucose” (2). In 2009, the International Expert Committee (IEC) recommended an HbA1c definition of 42–46 mmol/mol (6.0–6.4%) for the intermediate risk group, which has been adopted by some organizations (5). Identification of individuals with prediabetes provides an opportunity for intervention through lifestyle modification and pharmacologic interventions to prevent progression to diabetes (6,7). Consensus on definitions of prediabetes could help guide resource allocation and aid public health efforts focused on identification of persons at risk for diabetes and its complications.

Although the selection of biomarker cut-points for screening or diagnosis requires a broad range of considerations, associations with clinical outcomes are an important factor (8). Therefore, the objective of this study was to compare the prognostic performance of the above-mentioned definitions of prediabetes in their associations with major clinical

complications including incident diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality. We compared the risk of future outcomes across different definitions of fasting glucose, HbA1c and 2-hour glucose during over two decades of follow-up in the community-based Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population

The ARIC study originally enrolled 15,792 adults aged 45–64 from Jackson, Mississippi; Forsyth County, North Carolina; suburban Minneapolis, Minnesota; and Washington County, Maryland. Detailed methods of the study have been previously published (9). Briefly, the first examination took place from 1987 to 1989, with 3 follow-up visits approximately every 3 years, and a fifth visit from 2011 to 2013.

Institutional review board approval was acquired at all study sites and written consent was obtained from all participants. We conducted two main comparisons. First, with visit 2 (1990 to 1992) as baseline, when both fasting glucose and HbA1c were measured. And, second, with visit 4 (1996 to 1998) as baseline, when both fasting glucose and 2-hour glucose were measured. Our final sample size included 10,844 participants who attended visit 2 and 7,194 participants who attended visit 4 (see eFigure 1 for details).

Measurements of Hyperglycemia and Definitions of Prediabetes

Fasting glucose was measured using a hexokinase method in serum at visit 2 and in plasma at visit 4. We conducted a formal comparison and re-calibrated fasting glucose values to ensure equivalence of the measurements over time (10). HbA1c was measured in stored whole-blood samples from visit 2 by HPLC using the Tosoh A1c 2.2 Plus and Tosoh G7 methods, aligned to the Diabetes Control and Complications Trial (11). Two-hour glucose was measured following a 75-g oral glucose tolerance test administered at visit 4 (12). We defined prediabetes using three definitions recognized by the ADA: fasting glucose 5.6–6.9 mmol/L; HbA1c 39–46 mmol/mol; and 2-hour glucose 7.8–11.0 mmol/L, along with definitions recommended by the WHO: fasting glucose 6.1–6.9 mmol/L; and IEC: HbA1c 42–46 mmol/mol.

Assessment of Outcomes

Participants were prospectively followed for diabetes, chronic kidney disease, atherosclerotic cardiovascular disease (coronary heart disease and ischemic stroke), peripheral arterial disease, and all-cause mortality, loss to follow up, or end of follow up (2013). Incident diabetes was defined by self-report of a physician diagnosis of diabetes or use of glucose-lowering medication during a study visit or annual telephone call (13,14). Chronic kidney disease was defined by an estimated glomerular filtration rate measurement <60 mL/min/1.73 m^2 measured at a study visit and an eGFR decline from the baseline visit of at least 25% at the follow-up visit, or chronic kidney disease related hospitalization or death, or an end stage renal disease event identified by the United States Renal Data System registry (15). Incident atherosclerotic cardiovascular disease events were adjudicated and

included any coronary heart disease hospitalization or death, or ischemic stroke hospitalization or death. Peripheral arterial disease events were identified from hospitalization records (ICD-9 discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularization (38.18, 39.25, 39.29, 39.50). All-cause mortality was ascertained from hospital and National Death Index records.

Measurement of Covariates

Body mass index, waist-to-hip-ratio, blood pressure, lipids, and estimated glomerular filtration rate (calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration Equation [CKD-EPI]) (16) were measured per standard protocols (17–19). Age, sex, race-center (white, Minneapolis; black, Jackson; white, Washington County; black, Forsyth County; white, Forsyth County), education level, smoking status, alcohol use, parental history of diabetes, and use of lipid-lowering medications were reported at study visits. Hypertension was defined as an elevated systolic (≥ 140 mm Hg) or diastolic (≥ 90 mm Hg) blood pressure from the mean of two measurements taken at a study visit or the use of blood-pressure lowering medications.

Statistical Analysis

We compared baseline characteristics of the study participants at the relevant visit across clinical categories (normoglycemia, prediabetes, and undiagnosed diabetes) for the different definitions of prediabetes. We calculated sensitivity and specificity (and other related metrics) of each prediabetes definition using 10-year Kaplan-Meier estimates comparing those with prediabetes to those with normoglycemia against those with and without the events of interest. Cox proportional hazards models were used to estimate adjusted hazard ratios of incident events associated with the different clinical categories, with normoglycemia as the reference group. Demographic adjusted models included age, sex, and race-center. Fully adjusted models included all variables in demographic adjusted models plus education level, body mass index, waist-to-hip ratio, total cholesterol, HDL-cholesterol, triglycerides, eGFR, hypertension, smoking status, alcohol use, lipid-lowering medication use, and family history of diabetes. We used Harrell's C-statistic to compare discrimination of models with the different clinical categories with respect to future outcomes and obtained 95% confidence intervals with a jackknife approach (20). We calculated the continuous Net Reclassification Index (cNRI) for 10-year risk of each outcome for the different clinical categories, using ADA fasting glucose as the reference. We conducted sensitivity analyses stratifying by race and sex and also after excluding those with undiagnosed diabetes (21).

As an ancillary analysis, we replicated our study using data from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of the U.S. population to evaluate the generalizability of our results (Online Supplement 2). Only prospective information on fatal cardiovascular disease and all-cause mortality were available in NHANES. All analyses were conducted using Stata/SE version 13.

Role of the Funding Source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. All authors had access to the data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Persons identified by HbA1c-defined prediabetes were more often female, black, had less high school education, had more hypertension, and had a higher proportion of current smokers and a lower proportion of current drinkers compared to those with fasting glucose-defined prediabetes at visit 2 (Table 1). At visit 4, those with prediabetes defined by 2-hour glucose were more often female, less often black, and less often obese than those with fasting-glucose defined prediabetes, but otherwise had relatively similar baseline risk factors. Participant characteristics by the WHO fasting glucose and IEC HbA1c-defined prediabetes definitions are shown in the Online Supplement (eTable 1).

Prevalence differed across definitions of prediabetes (Table 2). At visit 2 (1990–1992, age range: 47 to 70), the prevalence of ADA fasting glucose-defined prediabetes was 37.9% (95%CI, 37.0, 38.8), compared to a prevalence of WHO fasting glucose-defined prediabetes of 11.2% (95%CI, 10.6, 11.8), ADA HbA1c-defined prediabetes of 18.7% (95%CI, 18.0, 19.4), and IEC HbA1c-defined prediabetes of 9.0% (95%CI, 8.4, 9.5). At visit 4 (1996–1998, age range: 53 to 76), the prevalence of ADA fasting glucose-defined prediabetes was 29.8% (95%CI, 28.7, 30.8), while the prevalence of WHO fasting glucose-defined prediabetes was 8.6% (95%CI, 8.0, 9.3), and ADA/WHO 2-hour glucose-defined prediabetes was 27.9% (95%CI, 26.9, 29.0). The cross-tabulations of the different definitions are shown in the Online Supplement (eTable 2).

Of the 10,844 participants included in the analyses with visit 2 at baseline, there were 3,152 incident cases of diabetes, 2,608 incident chronic kidney disease cases, 1,556 incident atherosclerotic cardiovascular events, 266 incident peripheral arterial disease cases, and 3,177 deaths, during approximately 22 years of follow-up. Of the 7,194 participants included in the analyses with visit 4 as baseline, there were 1,859 incident cases of diabetes, 1,444 incident chronic kidney disease cases, 760 incident atherosclerotic cardiovascular events, 115 incident peripheral arterial disease cases, and 1,568 deaths during approximately 16 years of follow up (eTable 3).

Comparing the sensitivity and specificity for each definition of prediabetes for 10-year risk of each outcome revealed that the IEC and ADA HbA1c and WHO fasting glucose prediabetes definitions had higher specificity for all outcomes, while the ADA fasting glucose and ADA/WHO 2-hour glucose prediabetes definitions were more sensitive (Table 3). IEC and ADA HbA1c and WHO fasting glucose had higher positive predictive values and negative likelihood ratios for incident diabetes and higher positive likelihood ratios for all outcomes compared to ADA fasting glucose. Negative predictive values were similar across outcomes.

In age, sex, and race-adjusted Cox proportional hazards models, prediabetes by all five definitions were significantly associated with risk of future clinical outcomes (Table 4). Prediabetes defined by HbA1c-based definitions had higher incidence rates, larger hazard ratios, and higher C-statistics for chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality, than prediabetes defined by fasting glucose (Table 4; eTables 3–5). Adjusting for additional risk factors did not appreciably alter our findings (eTable 4). The differences in the C-statistics comparing the HbA1c- and glucose-based definitions, although statistically significant, were small (improvement in the C-statistic was generally less than 0.02). ADA HbA1c-defined prediabetes also demonstrated significant overall improvement in the cNRI for atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality compared to fasting glucose-defined prediabetes (eTable 6). The cNRI results show that the improvement was modest and primarily driven by the correct reclassification of non-events, consistent with the higher specificity of the HbA1c-based definitions as compared to fasting glucose.

For incident diabetes, after demographic adjustment, the IEC HbA1c definition had the largest hazard ratio, but the ADA fasting glucose definition had a significant but modestly higher C-statistic and better classified those at risk for future incident diabetes based on overall cNRI improvement (Table 4; eTable 5; eTable 6). However, after adjustment for additional risk factors (fully adjusted model), there was no longer a significant difference in the C-statistics for ADA clinical categories for diabetes compared to the other definitions (eTable 5).

The hazard ratios and C-statistics for all outcomes were similar when comparing all ADA and WHO glucose prediabetes definitions, with the exception of incident diabetes. For incident diabetes, there were statistically significant but modest differences across ADA and WHO definitions (eTable 5). However, these differences did not persist after adjustment for additional risk factors (fully adjusted model).

Excluding those with undiagnosed diabetes did not appreciably alter our findings (eTables 7–8). We did not observe consistent differences in results across outcomes in analyses by race, with the exception of incident diabetes (eTables 9–10). Across all definitions, blacks were less likely to report a subsequent diagnosis of diabetes or glucose lowering-medication use during follow-up compared to whites in the demographic adjusted model (all p-for-interaction <0.05) (eTable 9). After adjustment for additional risk factors (fully adjusted model), the black-white difference was attenuated although the interaction for some definitions remained statistically significant (eTable 10). In analyses stratified by sex, there was moderate evidence for a stronger association of prediabetes and undiagnosed diabetes with peripheral arterial disease in women compared to men for both HbA1c- and fasting-glucose based definitions (eTables 11–12). In contrast, 2-hour glucose was not significantly associated with incident peripheral arterial disease in either men or women. Mortality associations, regardless of definition, were also somewhat stronger in women compared to men.

Our ancillary analysis in NHANES III (Online Supplement 2) demonstrated similar patterns in prevalence, sensitivity, and specificity for the different definitions of prediabetes. For all-cause mortality, patterns in hazard ratios and Harrell's C-statistic were also similar. For fatal cardiovascular disease, hazard ratios for IEC HbA1c-defined prediabetes were the largest, followed by ADA fasting glucose, ADA HbA1c, ADA/WHO 2-hour glucose and finally WHO fasting glucose.

Discussion

There are significant differences in prevalence and also performance of various definitions of prediabetes when judged by long-term complications. Use of ADA fasting glucose or ADA/WHO 2-hour glucose to define prediabetes resulted in higher prevalence estimates than WHO fasting glucose, ADA HbA1c, or IEC HbA1c-defined prediabetes. Indeed, using the ADA fasting glucose definition, over one third of the study population was estimated to have prediabetes. ADA HbA1c, IEC HbA1c, and WHO fasting glucose were the most specific definitions, with higher positive likelihood ratios, for identification of persons at risk for long-term clinical outcomes, while ADA fasting glucose and ADA/WHO 2-hour glucose were more sensitive. These differences in sensitivity and specificity have relevance for defining prediabetes in the setting of a screening program.

Differences in risk discrimination across prediabetes definitions were modest, but clinical categories based on HbA1c (ADA or IEC) performed slightly better than fasting glucose categories for microvascular and macrovascular outcomes. Net reclassification improvement also supported that a definition of ADA HbA1c prediabetes better classified those at risk for future cardiovascular and mortality outcomes. In minimally adjusted models, fasting glucose-defined prediabetes performed slightly better for prediction of future diabetes than HbA1c-defined prediabetes. This is not surprising as most cases of diabetes would have been identified by a health care provider during follow up on the basis of elevations in glucose (HbA1c was not recommended for diagnosis until 2009). Clinical categories of ADA and WHO fasting glucose and ADA/WHO 2-hour glucose were generally similar to each other for risk discrimination of clinical outcomes.

Across all clinical categories, whether defined by fasting glucose, HbA1c, or 2-hour glucose, blacks were less likely to report a diagnosis of diabetes or diabetes medication use during follow-up. This suggests that for the same level of hyperglycemia, blacks may be more likely to have delays in diagnosis, reflecting disparities in socioeconomic status and/or access to care. There was little evidence for race-interaction for the other clinical outcomes.

Our findings complement existing evidence and extend previous findings in ARIC. An earlier study in ARIC found that fasting glucose 5.6–6.9 mmol/L and 2-hour glucose 7.8–11.0 mmol/L had similar associations with incident cardiovascular disease and all-cause mortality during a median follow up time of 6.3 years (22). Our results confirm these findings, but with approximately 10 more years of follow up and many more incident events. Our findings are also consistent with results from the Emerging Risk Factors Collaboration (ERFC), a 73-study participant-level meta-analysis of 294,998 individuals. The ERFC found that covariate-adjusted HbA1c performed as well as random glucose and better than fasting

and 2-hour glucose with respect to hazard ratios, and as well as fasting glucose and better than random and 2-hour glucose with respect to C-statistics for prediction of cardiovascular disease (23).

By contrast, the 2001 DECODE Study of 22,514 participants from 10 different European centers followed for 8.8 years, found that 2-hour glucose was more strongly associated with atherosclerotic cardiovascular death and all-cause mortality as compared to fasting glucose (24). We do note that DECODE collected measurements in different blood specimens (plasma, whole blood) across the 10 European centers. Methodological and study population differences notwithstanding, it is unclear why our results do not agree with the DECODE findings. Meta-analyses have also shown conflicting results as to whether impaired fasting glucose or impaired glucose tolerance is more strongly associated with cardiovascular disease outcomes (25,26).

Several limitations of our study should be considered in the interpretation of our findings. First, we did not have concurrent measurements of fasting glucose, HbA1c, and 2-hour glucose. Second, as part of the ARIC Study protocol, abnormal lab values including elevated fasting glucose (> 11.1 mmol/L) or 2-hour glucose (> 16.7 mmol/L) were reported back to the participants. Thus, approximately 0.52% of participants following visit 2 and 0.49% of participants following visit 4 received reports for elevated fasting glucose and 1.22% of participants following visit 4 received reported for elevated 2-hour glucose. HbA1c results at visit 2 were not reported as it was measured retrospectively (>10 years after sample collection). The reporting of the glucose measures to participants may have increased the probability of a diagnosis of diabetes (27). Third, we utilized a definition of incident diabetes based on self-report. Fourth, our findings may not be generalizable beyond black and white Americans. Fifth, despite the large sample size and number of events, the possibility exists that we may have been underpowered to detect moderate differences between definitions, particularly given the overlap of definitions. Finally, while our results in ARIC were relatively consistent with those for all-cause and cardiovascular mortality in NHANES III, further replication, especially for other major complications in diverse populations, is warranted. Strengths of this study included our ability to compare the prognostic value of multiple definitions of prediabetes, rigorous assessment of glycemia and related risk factors using standardized protocols and trained personnel, active surveillance for major clinical complications, and over two decades of follow-up in a large, community-based population.

When deciding among definitions of prediabetes, a number of considerations will need to be weighed and the optimal choice will depend on screening objectives. Long-term risk associations, along with considerations such as cost, availability, and the specific strengths and weaknesses of each biomarker are all relevant. It is difficult to weigh whether a strategy that would identify large numbers of persons, including many at relatively low risk of future outcomes, might be more beneficial than strategies that are highly specific but may miss some high-risk individuals who should receive preventative interventions. Prediabetes defined by ADA HbA1c, IEC HbA1c, and WHO fasting glucose identified fewer people, but were more specific definitions for identification of persons at risk for long-term outcomes. HbA1c-based definitions had higher relative risk associations and showed small but

statistically significant improvements in risk discrimination for a broad range of clinical complications. Whereas ADA fasting glucose-defined prediabetes was more sensitive, it was associated with lower long-term risks. With respect to long-term prediction of clinical outcomes, prediabetes definitions based on 2-hour glucose did not demonstrate appreciably better discrimination over fasting glucose for chronic kidney disease or cardiovascular outcomes. The comparative utility of different definitions of prediabetes will vary depending on the goals of the screening program, however data on long-term prognostic performance can and should help to inform use and recommendations regarding different definitions of prediabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline characteristics of ARIC participants without a history of cardiovascular disease or diagnosed diabetes by different definitions of prediabetes *

	Normoglycemia	Prediabetes	Undiagnosed diabetes	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA fasting glucose clinical categories			ADA HbA1c clinical categories		
Visit 2 (1990–92)	**< 5.6 mmol/L**	**5.6–6.9 mmol/L**	**≥ 7.0 mmol/L**	**< 39 mmol/mol**	**39–46 mmol/mol**	**≥ 48 mmol/mol**
N = 10,844	**n = 6,215**	**n = 4,112**	**n = 517**	**n = 8,355**	**n = 2,027**	**n = 462**
Age (years)	56.8 (5.6)	57.6 (5.7)	57.7 (5.6)	56.8 (5.6)	58.2 (5.6)	58.1 (5.6)
Female, %	63.2	47.8	54.4	57.4	54.2	61.5
Black, %	17.3	25.1	37.3	15.0	40.4	49.8
Less than high school education, %	16.3	21.3	28.1	15.6	28.9	32.3
Body Mass Index (kg/m^2)	26.4 (4.8)	28.9 (5.2)	31.6 (6.1)	27.0 (4.8)	29.3 (5.8)	32.3 (6.3)
Obese (≥ 30 kg/m^2), %	18.8	34.5	54.4	21.7	38.4	59.5
Waist-to-hip ratio	0.90 (0.1)	0.94 (0.1)	0.97 (0.1)	0.91 (0.1)	0.94 (0.1)	0.97 (0.1)
Fasting glucose (mmol/L)	5.11 (0.3)	5.98 (0.4)	8.62 (2.5)	5.39 (0.5)	5.89 (0.7)	8.29 (2.9)
HbA1c (mmol/mol)	34.9 (4.2)	37.6 (4.8)	52.7 (17)	34.3 (3.1)	41.9 (1.9)	57.6 (15.6)
Hypercholesterolemia, %	74.0	81.7	87.6	75.8	82.8	87.9
Hypertension, %	24.5	37.8	54.6	26.9	42.4	53.9
Estimated glomerular filtration rate (mL/min/1.73 m ^{2})	97.3 (13)	96.9 (14)	99.7 (15)	96.8 (13)	98.2 (15)	101 (16)
Current smoker, %	21.6	21.6	19.7	19.8	27.9	23.6
Current drinker, %	60.8	59.2	54.2	63.3	50.0	41.8
Family history of diabetes, %	20.3	24.6	33.7	21.3	25.2	34.0
	ADA fasting glucose clinical categories			**ADA/WHO 2-hour glucose clinical categories**		
Visit 4 (1996–98)	**< 5.6 mmol/L**	**5.6–6.9 mmol/L**	**≥ 7.0 mmol/L**	**< 7.8 mmol/L**	**7.8–11.0 mmol/L**	**≥ 11.0 mmol/L**
N = 7,194	**n = 4,720**	**n = 2,142**	**n = 332**	**n = 4,442**	**n = 2,009**	**n = 743**
Age (years)	62.7 (5.5)	62.9 (5.5)	63.1 (5.4)	62.1 (5.4)	63.6 (5.6)	64.3 (5.5)
Female, %	63.2	47.8	51.8	55.4	62.5	62.1
Black, %	14.5	21.2	25.6	17.1	15.4	20.5
Less than high school education, %	13.6	18.2	23.2	13.6	17.0	21.7
Body Mass Index (kg/m^2)	27.4 (5.0)	30.1 (5.3)	32.1 (6.0)	27.7 (5.1)	29.2 (5.3)	30.5 (5.6)

	Normoglycemia	Prediabetes	Undiagnosed diabetes	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA fasting glucose clinical categories			ADA HbA1c clinical categories		
Visit 2 (1990–92)	**< 5.6 mmol/L**	**5.6–6.9 mmol/L**	**≥ 7.0 mmol/L**	**< 39 mmol/mol**	**39–46 mmol/mol**	**≥ 48 mmol/mol**
N = 10,844	**n = 6,215**	**n = 4,112**	**n = 517**	**n = 8,355**	**n = 2,027**	**n = 462**
Obese (≥ 30 kg/m^2), %	24.0	45.1	60.2	26.2	38.5	48.7
Waist-to-hip ratio	0.93 (0.1)	0.97 (0.1)	0.98 (0.1)	0.93 (0.1)	0.95 (0.1)	0.97 (0.1)
Fasting glucose (mmol/L)	5.09 (0.3)	6.00 (0.3)	8.72 (2.5)	5.26 (0.5)	5.54 (0.6)	7.06 (2.3)
2-hour glucose (mmol/L)	6.76 (2.0)	8.23 (2.5)	14.8 (4.3)	5.84 (1.1)	9.10 (0.9)	13.7 (3.0)
Hypercholesterolemia, %	73.6	82.5	87.7	73.4	81.0	86.7
Hypertension, %	36.1	47.8	60.5	34.3	47.9	59.5
Estimated glomerular filtration rate (mL/min/1.73 m ^{2})	88.2 (12)	88.3 (13)	89.6 (12)	88.1 (12)	88.5 (13)	88.7 (13)
Current smoker, %	14.0	14.4	11.8	15.6	11.7	10.8
Current drinker, %	55.2	55.3	49.1	57.8	51.7	46.7
Family history of diabetes, %	19.8	26.3	33.1	19.2	26.2	30.8

*Mean (SD) unless otherwise indicated

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; WHO, World Health Organization

TABLE 2

Prevalence (95% confidence interval) of prediabetes by definition

	Prevalence (95%CI)
Visit 2 (1990–92)	
ADA fasting glucose, 5.6–6.9 mmol/L	37.9 (37.0, 38.8)
WHO fasting glucose, 6.1–6.9 mmol/L	11.2 (10.6, 11.8)
ADA HbA1c, 39–46 mmol/mol	18.7 (18.0, 19.4)
IEC HbA1c, 42–46 mmol/mol	8.95 (8.42, 9.50)
Visit 4 (1996–98)	
ADA fasting glucose, 5.6–6.9 mmol/L	29.8 (28.7, 30.8)
WHO fasting glucose, 6.1–6.9 mmol/L	8.63 (8.00, 9.30)
ADA/WHO 2-hour glucose, 7.8–11.0 mmol/L	27.9 (26.9, 29.0)

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; IEC, International Expert Committee; WHO, World Health Organization

TABLE 3

10-year sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio and corresponding 95% confidence intervals of incident clinical outcomes according to different definitions of prediabetes (vs. normoglycemia) at baseline

	Visit 2 (1990–92)				Visit 4 (1996–98)		
Outcome	**ADA fasting glucose 5.6–6.9 mmol/L**	**WHO fasting glucose 6.1–6.9 mmol/L**	**ADA HbA1c 39–46mmol/mol**	**IEC HbA1c 42–46mmol/mol**	**ADA fasting glucose 5.6–6.9 mmol/L**	**WHO fasting glucose 6.1–6.9 mmol/L**	**ADA/WHO 2-hour glucose 7.8–11.0 mmol/L**
Incident diabetes							
Sensitivity	0.73 (0.70, 0.76)	0.41 (0.37, 0.44)	0.52 (0.49, 0.55)	0.34 (0.31, 0.37)	0.61 (0.58, 0.64)	0.28 (0.26, 0.31)	0.55 (0.51, 0.58)
Specificity	0.63 (0.62, 0.64)	0.91 (0.90, 0.91)	0.83 (0.83, 0.84)	0.93 (0.92, 0.93)	0.74 (0.73, 0.75)	0.94 (0.94, 0.95)	0.72 (0.71, 0.73)
PPV	0.15 (0.14, 0.16)	0.28 (0.26, 0.31)	0.22 (0.21, 0.24)	0.31 (0.28, 0.34)	0.28 (0.26, 0.30)	0.44 (0.40, 0.48)	0.21 (0.20, 0.23)
NPV	0.96 (0.96, 0.97)	0.95 (0.94, 0.95)	0.95 (0.95, 0.96)	0.94 (0.93, 0.94)	0.92 (0.91, 0.93)	0.89 (0.88, 0.90)	0.92 (0.91, 0.93)
+LR	1.98 (1.89, 2.08)	4.41 (3.97, 4.89)	3.14 (2.90, 3.39)	4.81 (4.28, 5.41)	2.34 (2.19, 2.50)	4.84 (4.19, 5.58)	1.96 (1.82, 2.12)
-LR	0.43 (0.38, 0.48)	0.66 (0.64, 0.69)	0.58 (0.54, 0.62)	0.71 (0.68, 0.74)	0.52 (0.48, 0.57)	0.76 (0.73, 0.79)	0.63 (0.58, 0.68)
Chronic kidney disease							
Sensitivity	0.48 (0.43, 0.53)	0.18 (0.14, 0.23)	0.31 (0.27, 0.37)	0.15 (0.11, 0.19)	0.37 (0.31, 0.44)	0.15 (0.11, 0.20)	0.32 (0.26, 0.39)
Specificity	0.61 (0.60, 0.61)	0.89 (0.88, 0.89)	0.81 (0.80, 0.82)	0.91 (0.90, 0.91)	0.69 (0.68, 0.70)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)
PPV	0.04 (0.04, 0.05)	0.05 (0.04, 0.07)	0.05 (0.05, 0.07)	0.05 (0.04, 0.07)	0.04 (0.03, 0.05)	0.06 (0.04, 0.08)	0.03 (0.03, 0.04)
NPV	0.97 (0.97, 0.97)	0.97 (0.96, 0.97)	0.97 (0.97, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)
+LR	1.21 (1.08, 1.35)	1.58 (1.27, 1.98)	1.64 (1.40, 1.92)	1.60 (1.24, 2.08)	1.20 (1.01, 1.42)	1.72 (1.26, 2.35)	1.03 (0.85, 1.26)
-LR	0.86 (0.78, 0.95)	0.92 (0.88, 0.97)	0.85 (0.79, 0.91)	0.94 (0.90, 0.98)	0.91 (0.83, 1.01)	0.93 (0.88, 0.98)	0.99 (0.90, 1.08)
Atherosclerotic cardiovascular disease							
Sensitivity	0.47 (0.43, 0.52)	0.16 (0.13, 0.19)	0.34 (0.30, 0.39)	0.18 (0.15, 0.21)	0.39 (0.34, 0.44)	0.12 (0.09, 0.16)	0.32 (0.28, 0.37)
Specificity	0.61 (0.60, 0.62)	0.89 (0.88, 0.89)	0.81 (0.81, 0.82)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)	0.91 (0.90, 0.92)	0.69 (0.68, 0.70)
PPV	0.06 (0.06, 0.07)	0.07 (0.06, 0.09)	0.09 (0.08, 0.11)	0.10 (0.08, 0.12)	0.07 (0.06, 0.08)	0.07 (0.06, 0.10)	0.06 (0.05, 0.07)
NPV	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.96 (0.95, 0.96)	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.94 (0.94, 0.95)	0.95 (0.94, 0.95)
+LR	1.20 (1.10, 1.32)	1.36 (1.11, 1.66)	1.84 (1.63, 2.08)	2.03 (1.68, 2.45)	1.25 (1.10, 1.43)	1.36 (1.03, 1.79)	1.04 (0.89, 1.21)
-LR	0.87 (0.80, 0.94)	0.95 (0.92, 0.99)	0.81 (0.76, 0.86)	0.90 (0.87, 0.94)	0.89 (0.82, 0.96)	0.97 (0.93, 1.00)	0.98 (0.91, 1.06)
Peripheral arterial disease							
Sensitivity	0.54 (0.41, 0.66)	0.19 (0.11, 0.31)	0.30 (0.20, 0.43)	0.14 (0.06, 0.24)	0.42 (0.29, 0.57)	0.08 (0.02, 0.19)	0.37 (0.24, 0.51)

	Visit 2 (1990–92)				Visit 4 (1996–98)		
Outcome	**ADA fasting glucose 5.6–6.9 mmol/L**	**WHO fasting glucose 6.1–6.9 mmol/L**	**ADA HbA1c 39–46mmol/mol**	**IEC HbA1c 42–46mmol/mol**	**ADA fasting glucose 5.6–6.9 mmol/L**	**WHO fasting glucose 6.1–6.9 mmol/L**	**ADA/WHO 2-hour glucose 7.8–11.0 mmol/L**
Specificity	0.60 (0.59, 0.61)	0.88 (0.88, 0.89)	0.81 (0.80, 0.81)	0.91 (0.90, 0.91)	0.69 (0.68, 0.70)	0.91 (0.90, 0.92)	0.69 (0.68, 0.70)
PPV	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.01)
NPV	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)
+LR	1.35 (1.08, 1.69)	1.66 (1.02, 2.71)	1.56 (1.08, 2.25)	1.46 (0.80, 2.69)	1.36 (0.99, 1.87)	0.85 (0.33, 2.18)	1.17 (0.82, 1.68)
-LR	0.77 (0.59, 0.99)	0.91 (0.81, 1.03)	0.87 (0.74, 1.01)	0.95 (0.87, 1.05)	0.84 (0.66, 1.06)	1.02 (0.94, 1.10)	0.92 (0.75, 1.13)
All-cause mortality							
Sensitivity	0.46 (0.42, 0.49)	0.15 (0.12, 0.17)	0.31 (0.27, 0.35)	0.16 (0.13, 0.18)	0.35 (0.31, 0.39)	0.13 (0.10, 0.15)	0.33 (0.29, 0.37)
Specificity	0.61 (0.60, 0.62)	0.89 (0.88, 0.89)	0.81 (0.81, 0.82)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)
PPV	0.08 (0.07, 0.08)	0.08 (0.07, 0.10)	0.11 (0.09, 0.12)	0.11 (0.09, 0.13)	0.10 (0.08, 0.11)	0.12 (0.10, 0.15)	0.09 (0.08, 0.11)
NPV	0.94 (0.93, 0.95)	0.94 (0.93, 0.94)	0.94 (0.94, 0.95)	0.94 (0.93, 0.94)	0.92 (0.91, 0.92)	0.92 (0.91, 0.92)	0.92 (0.91, 0.93)
+LR	1.15 (1.06, 1.26)	1.26 (1.04, 1.53)	1.65 (1.46, 1.86)	1.74 (1.45, 2.10)	1.12 (0.99, 1.25)	1.43 (1.14, 1.80)	1.07 (0.95 1.21)
-LR	0.90 (0.84, 0.97)	0.97 (0.94, 1.00)	0.85 (0.81, 0.90)	0.93 (0.90, 0.96)	0.95 (0.89, 1.01)	0.96 (0.93, 0.99)	0.97 (0.91, 1.03)

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; PPV, positive predictive value; NPV, negative predictive value; WHO, World Health Organization; +LR, positive likelihood ratio, -LR, negative likelihood ratio

TABLE 4

Demographic adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes

		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality HR
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	(95% CI)
Visit 2 (1990–92)						
ADA fasting glucose definition	**< 5.6 mmol/L**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6–6.9 mmol/L	2.91 (2.69, 3.15) *	1.17 (1.08, 1.27) *	1.24 (1.12, 1.38) *	1.34 (1.03, 1.74) *	1.12 (1.04, 1.21) *
	≥ 7.0 mmol/L ‡	19.7 (17.6, 22.2) *	1.75 (1.49, 2.05) *	2.10 (1.74, 2.53) *	3.40 (2.30, 5.01) *	1.55 (1.35, 1.79) *
	C-statistic (95% CI)	0.713 (0.704, 0.723)	0.636 (0.625, 0.647)	0.662 (0.649, 0.676)	0.701 (0.670, 0.733)	0.683 (0.674, 0.692)
WHO fasting glucose definition	**< 6.1 mmol/L**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1–6.9 mmol/L	3.81 (3.48, 4.16) *	1.28 (1.14, 1.43) *	1.22 (1.05, 1.41) *	1.35 (0.95, 1.92)	1.25 (1.13, 1.38) *
	≥ 7.0 mmol/L ‡	14.5 (13.0, 16.2) *	1.69 (1.45, 1.97) *	1.95 (1.63, 2.34) *	3.09 (2.14, 4.47) *	1.52 (1.32, 1.75) *
	C-statistic (95% CI)	0.693 (0.683, 0.703)	0.636 (0.625, 0.647)	0.660 (0.646, 0.673)	0.700 (0.668, 0.732)	0.683 (0.674, 0.693)
ADA HbA1c definition	**< 39 mmol/mol**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39–46 mmol/mol	3.42 (3.15, 3.72) *	1.42 (1.29, 1.57) *	1.70 (1.51, 1.92) *	1.84 (1.37, 2.47) *	1.49 (1.37, 1.62) *
	≥ 48 mmol/mol ‡	20.8 (18.4, 23.4) *	2.04 (1.73, 2.40) *	2.40 (1.98, 2.90) *	5.38 (3.75, 7.73) *	1.81 (1.57, 2.10) *
	C-statistic (95% CI)	0.693 (0.683, 0.703)	0.640 (0.629, 0.651)	0.672 (0.659, 0.685)	0.722 (0.690, 0.754)	0.688 (0.679, 0.697)
IEC HbA1c definition	**< 42 mmol/mol**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42–46 mmol/mol	4.14 (3.74, 4.58) *	1.50 (1.32, 1.70) *	1.91 (1.65, 2.21) *	1.95 (1.34, 2.82) *	1.56 (1.40, 1.73) *
	≥ 48 mmol/mol ‡	17.9 (15.9, 20.2) *	1.96 (1.67, 2.30) *	2.27 (1.88, 2.74) *	4.99 (3.49, 7.11) *	1.73 (1.50, 1.99) *
	C-statistic (95% CI)	0.669 (0.659, 0.680)	0.639 (0.628, 0.650)	0.668 (0.655, 0.682)	0.718 (0.686, 0.750)	0.687 (0.678, 0.696)
Visit 4 (1996–98)						
ADA fasting glucose definition	**< 5.6 mmol/L**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6–6.9 mmol/L	3.43 (3.10, 3.80) *	1.08 (0.96, 1.21)	1.25 (1.07, 1.45) *	1.09 (0.73, 1.63)	1.15 (1.03, 1.28) *
	≥ 7.0 mmol/L ‡	25.3 (21.9, 29.2) *	1.45 (1.16, 1.82) *	1.79 (1.36, 2.37) *	1.99 (1.02, 3.88) *	1.68 (1.37, 2.05) *
	C-statistic (95% CI)	0.726 (0.714, 0.738)	0.624 (0.609, 0.639)	0.660 (0.641, 0.680)	0.707 (0.660, 0.754)	0.686 (0.673, 0.699)
WHO fasting glucose definition	**< 6.1 mmol/L**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)

		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality HR
		HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**(95% CI)**
	6.1–6.9 mmol/L	4.48 (3.97, 5.05) *	1.23 (1.04, 1.47) *	1.10 (0.87, 1.40)	0.63 (0.29, 1.35)	1.29 (1.10, 1.51) *
	≥ **7.0 mmol/L** ≠	18.5 (16.2, 21.2) *	1.45 (1.16, 1.81) *	1.67 (1.27, 2.20) *	1.85 (0.96, 3.56)	1.65 (1.35, 2.01) *
	C-statistic (95% CI)	0.694 (0.681, 0.708)	0.625 (0.610, 0.640)	0.658 (0.638, 0.677)	0.710 (0.662, 0.757)	0.687 (0.673, 0.700)
ADA/WHO 2-hour glucose definition	**< 7.8 mmol/L**	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8–11.0 mmol/L	2.56 (2.30, 2.86) *	1.16 (1.03, 1.31) *	1.08 (0.92, 1.27)	0.83 (0.54, 1.29)	1.17 (1.05, 1.31) *
	≥ **11.0 mmol/L** ≠	10.6 (9.41, 11.9) *	1.39 (1.18, 1.63) *	1.44 (1.17, 1.78) *	0.93 (0.50, 1.72)	1.33 (1.15, 1.55) *
	C-statistic (95% CI)	0.728 (0.716, 0.741)	0.626 (0.611, 0.641)	0.659 (0.639, 0.678)	0.705 (0.658, 0.752)	0.685 (0.672, 0.698)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

≠ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; IEC, International Expert Committee; HbA1c, hemoglobin A1c; HR, hazard ratio; WHO, World Health Organization

Outcome Definitions: Incident diabetes: self-report of a physician diagnosis of diabetes or use of glucose-lowering medication during a study visit or annual telephone call; Chronic kidney disease: subsequent estimated glomerular filtration rate (eGFR) measurement < 60 mL/min/1.73 m^2 measured at a study visit and an eGFR decline from baseline visit of at least 25% at the follow-up visit, or chronic kidney disease related hospitalization or death, or an end stage renal disease event identified by the United States Renal Data System registry; Atherosclerotic cardiovascular disease: any coronary heart disease hospitalization and death and ischemic stroke hospitalization and death (adjudicated events); Peripheral arterial disease: events identified from hospitalization records (International Classification of Disease, Ninth Revision (ICD-9) discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularization (38.18, 39.25, 39.29, 39.50); All-cause mortality: ascertained from hospital and National Death Index records