Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study

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Lancet Diabetes Endocrinol 2017; 5: 34–42

Published Online November 15, 2016 http://dx.doi.org/10.1016/S2213-8587(16)30321-7

See Comment page 5

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Summary

Background No consensus on definitions of prediabetes exists among international organisations. Analysis of associations with different definitions and clinical complications can inform the comparative value of different prediabetes definitions. We compared the risk of future outcomes across different prediabetes definitions based on fasting glucose concentration, HbA_{1c}, and 2 h glucose concentration during over two decades of follow-up in the community-based Atherosclerosis Risk in Communities (ARIC) study. We aimed to analyse the associations of definitions with outcomes to provide a comparison of different definitions.

Methods We did a prospective cohort study of participants in the ARIC study who did not have diagnosed diabetes and who attended visit 2 (1990–92; n=10 844) and who attended visit 4 (1996–98; n=7194). ARIC participants were enrolled from four communities across the USA. Fasting glucose concentration and HbA_{1c} were measured at visit 2 and fasting glucose concentration and 2 h glucose concentration were measured at visit 4. We compared prediabetes definitions based on fasting glucose concentration (American Diabetes Association [ADA] fasting glucose concentration cutoff 5·6–6·9 mmol/L and WHO fasting glucose concentration cutoff 6·1–6·9 mmol/L), HbA_{1c} (ADA HbA_{1c} cutoff 5·7–6·4% [39–46 mmol/mol] and International Expert Committee [IEC] HbA_{1c} cutoff 6·0–6·4% [42–46 mmol/mol]), and 2 h glucose concentration (ADA and WHO 2 h glucose concentration cutoff 7·8–11·0 mmol/L).

Findings Prediabetes defined using the ADA fasting glucose concentration cutoff (prevalence 4112 [38%] of 10 844 people; 95% CI 37·0–38·8) was the most sensitive for major clinical outcomes, whereas using the ADA HbA_{1c} cutoff (2027 [19%] of 10 884 people; 18·0–19·4) and IEC HbA_{1c} cutoff (970 [9%] of 10 844 people; 8·4–9·5), and the WHO fasting glucose concentration cutoff (1213 [11%] of 10 844 people; 10·6–11·8) were more specific. After demographic adjustment, HbA_{1c}-based definitions of prediabetes had higher hazard ratios and better risk discrimination for chronic kidney disease, cardiovascular disease, peripheral arterial disease, and all-cause mortality than did fasting glucose concentration-based definitions (all $p<0·05$). The C-statistic for incident chronic kidney disease was 0·636 for ADA fasting glucose concentration clinical categories and 0·640 for ADA HbA_{1c} clinical categories (difference –0·005, 95% CI –0·008 to –0·001). The C-statistics were 0·662 for ADA fasting glucose clinical concentration categories and 0·672 for ADA HbA_{1c} clinical categories for atherosclerotic cardiovascular disease, 0·701 for ADA fasting glucose concentration clinical categories and 0·722 for ADA HbA_{1c} clinical categories for peripheral arterial disease, and 0·683 for ADA fasting glucose concentration clinical categories and 0·688 for ADA HbA_{1c} clinical categories for all-cause mortality. Prediabetes defined using the ADA HbA_{1c} cutoff showed a significant overall improvement in the net reclassification index for cardiovascular outcomes and death compared with prediabetes defined with glucose-based definitions. ADA fasting glucose concentration clinical categories, WHO fasting glucose concentration clinical categories, and ADA and WHO 2 h glucose concentrations clinical categories were not significantly different in terms of risk discrimination for chronic kidney disease, cardiovascular outcomes, or mortality outcomes.

Interpretation Our results suggest that prediabetes definitions using HbA_{1c} were more specific and provided modest improvements in risk discrimination for clinical complications. The definition of prediabetes using the ADA fasting glucose concentration cutoff was more sensitive overall.

Funding US National Institutes of Health.

Introduction

Prediabetes is a pressing clinical and public health problem that affects approximately 12–30% of US adults aged 18 years and older, depending on the definition used.[1] International organisations largely agree on the clinical cutoff points for diagnosis of diabetes and, in 2010, HbA_{1c} ≥6·5% (≥48 mmol/mol) was adopted for diagnosis of diabetes by many international groups, in part based on the association of HbA_{1c} with retinopathy.[2–5] By contrast, the category of prediabetes does not have a uniform definition. The American Diabetes Association (ADA) recommends using the following criteria to identify people with prediabetes: fasting glucose concentration between 5·6 and 6·9 mmol/L (100–125 mg/dL; impaired fasting glucose), HbA_{1c} of 5·7–6·4% (39–46 mmol/mol), or 2 h glucose concentration after a 75 g oral glucose

Research in context

Evidence before this study

We searched PubMed with the search terms "prediabetic state" OR "prediabetes", "impaired fasting glucose" OR "impaired glucose tolerance", AND "diabetes mellitus" OR "diabetes", OR "cardiovascular diseases" OR "chronic renal insufficiency" OR "chronic kidney disease", OR "peripheral vascular diseases" OR "peripheral arterial disease", OR "all-cause mortality" OR "mortality", AND "humans", for papers published up to June, 2015. There were no date or language restrictions. Prediabetes is characterised by elevated levels of blood glucose or hyperglycaemia that falls below the diagnostic threshold for diabetes. The prognostic value of different clinical definitions of prediabetes has not previously been formally compared. Current definitions include those by the American Diabetes Association (ADA), which defines prediabetes as a fasting glucose concentration of 5·6–6·9 mmol/L, an HbA_{1c} of 5·7–6·4% (39–46 mmol/L), or a 2 h glucose concentration of 7·8–11·0 mmol/L. WHO recommends the same 2 h glucose concentration cutoffs as the ADA, but recommends a fasting glucose concentration of 6·1–6·9 mmol/L as another definition for prediabetes. The International Expert Committee (IEC) defines prediabetes as an HbA_{1c} of 6·0–6·4% (42–46 mmol/L).

Added value of this study

We compared the prognostic value of the ADA, WHO, and IEC definitions of prediabetes in the Atherosclerosis Risk in Communities (ARIC) study, a large, prospective cohort study of over 10 000 middle-aged adults followed-up for over two decades for health outcomes including incident diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality. We found that WHO fasting glucose concentration cutoffs and HbA_{1c}-based definitions of prediabetes result in lower prevalence estimates than ADA fasting glucose concentration cutoffs and ADA and WHO 2 h glucose concentration cutoffs, but were more specific in identifying people at risk for long-term outcomes. We also observed that ADA fasting glucose concentration and ADA and WHO 2 h glucose concentration-based definitions of prediabetes are more sensitive for long-term outcomes. We found that HbA_{1c}-based definitions of prediabetes had stronger associations with long-term outcomes and provided modest, but statistically significantly more information for risk discrimination than fasting glucose-based definitions for many major clinical complications. We did not observe meaningful differences between definitions using both ADA and WHO fasting glucose concentrations compared with those using ADA and WHO 2 h glucose concentration cutoffs for long-term risk associations.

Implications of all the available evidence

Many considerations need to be accounted for in the selection of a definition of prediabetes for use in population screening or other settings, but long-term risk associations can and should be taken into account when reaching consensus on a definition for prediabetes.

tolerance test of 7·8–11·0 mmol/L (140–199 mg/dL; impaired glucose tolerance).[6] WHO also recommends 2 h glucose of 7·8–11·0 mmol/L to identify impaired glucose tolerance, but recommends a fasting glucose concentration 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 HbA_{1c} of 6·0–6·4% (42–46 mmol/mol) for the identification of an intermediate risk group, which has been adopted by some organisations.[5] Identification of individuals with prediabetes provides an opportunity for intervention through lifestyle modification and pharmacological interventions to prevent progression to diabetes.[6,7] Consensus on definitions of prediabetes could help guide resource allocation and aid public health efforts to identify people at risk of developing diabetes and its complications.

Although the selection of biomarker cutoff points for screening or diagnosis requires a broad range of considerations, associations with clinical outcomes are an important factor.[8] Therefore, the aim of this study was to compare the prognostic performance of the above-mentioned definitions of prediabetes in their associations with major clinical complications such as 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 prediabetes by fasting glucose concentration, HbA_{1c}, and 2 h glucose concentration during over two decades of follow-up in the community-based Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study design and participants

This prospective cohort study was based on the ARIC study, which originally enrolled 15792 adults aged 45–64 years from the communities of Jackson, MS; Forsyth County, NC; suburban Minneapolis, MN; and Washington County, MD, USA. We excluded participants with prevalent diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, or peripheral arterial disease, those who were missing variables of interest, or those who fasted for less than 10 h (see appendix for full details). Detailed methods of the study have been previously published.[9] Briefly, the first examination, including medical, social, and demographic assessment, took place from 1987 to 1989, with three follow-up visits approximately every 3 years, and a fifth visit between 2011 and 2013. Institutional review board approval was acquired at all study sites and written consent was obtained from all participants.

See Online for appendix

Procedures

We did two main comparisons. First, with visit 2 (1990–92) as baseline, when both fasting glucose concentration and HbA_{1c} were measured. And, second, with visit 4 (1996–98) as baseline, when both fasting glucose concentration and 2 h glucose concentration were measured. Our final sample size included 10 844 participants who attended visit 2 and 7194 participants who attended visit 4 (appendix). Fasting glucose was measured using a hexokinase method in serum at visit 2 and in plasma at visit 4. We formally compared and recalibrated fasting glucose concentrations to ensure equivalence of the measurements over time.[10] HbA_{1c} was measured in stored whole-blood samples from visit 2 by high-performance liquid chromatography using the Tosoh A_{1c} 2.2 Plus and Tosoh G7 methods (Tosoh Bioscience, San Francisco, CA, USA), aligned to those used in the Diabetes Control and Complications Trial.[11] 2 h plasma glucose concentration was measured following a 75 g oral glucose tolerance test administered using a hexokinase method at visit 4.[12] We defined prediabetes using three definitions recognised by the ADA: fasting glucose concentration cutoff 5·6–6·9 mmol/L, HbA_{1c} cutoff 5·7–6·4% (39–46 mmol/mol), and 2 h glucose cutoff 7·8–11·0 mmol/L, along with definitions recommended by WHO (fasting glucose concentration cutoff 6·1–6·9 mmol/L), and IEC (HbA_{1c} cutoff 6·0–6·4% [42–46 mmol/mol]).

Participants were prospectively followed up and incidents of diabetes, chronic kidney disease, atherosclerotic cardiovascular disease (coronary heart disease and ischaemic stroke), peripheral arterial disease, and all-cause mortality were recorded until end of follow-up in 2013 (loss to follow-up was also recorded). Incident diabetes was defined by self-report of a physician diagnosis of diabetes or use of glucose-lowering medication reported during a study visit or annual telephone call.[13,14] Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1·73 m^2 measured at a study visit and a reduction in eGFR of at least 25% from the baseline visit to the follow-up visit, or chronic kidney disease-related hospital admission or death by continuous active surveillance, or an end-stage renal disease event identified by the US Renal Data System registry.[15] Incident atherosclerotic cardiovascular disease events were adjudicated and included any coronary heart disease hospital admission or death, or ischaemic stroke hospital admission or death, and were obtained by continuous active surveillance. Peripheral arterial disease events were identified from hospital admission records (International Classification of Diseases 9 discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularisation (38.18, 39.25, 39.29, 39.50). All-cause mortality was ascertained from hospital and National Death Index records.

BMI, waist-to-hip ratio, blood pressure, lipid concentrations, and eGFR (calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration Equation)[16] were measured following standard protocols.[17–19] Age, sex, race centre (white, Minneapolis; black, Jackson; white, Washington County; black, Forsyth County; white, Forsyth County; as defined in the ARIC study design), 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 (normoglycaemia, prediabetes, and undiagnosed diabetes) for the different definitions of prediabetes. We calculated sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of each prediabetes definition using 10 year Kaplan-Meier estimates comparing people with prediabetes to those with normoglycaemia against people 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 normoglycaemia as the reference group. Demographic-adjusted models included age, sex, and race centre. Fully adjusted models included all variables in demographic-adjusted models plus education level, BMI, waist-to-hip ratio, total cholesterol concentration, HDL cholesterol concentration, triglyceride concentrations, 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% CIs 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 prediabetes defined using ADA fasting glucose concentration cutoffs as the reference. We did sensitivity analyses stratifying by race and sex and after excluding people 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 US population, to assess the generalisability of our results (appendix). Only prospective information on fatal cardiovascular disease and all-cause mortality was available in NHANES. All analyses were done using Stata/SE (version 13).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data and the

corresponding author had final responsibility to submit for publication.

Results

In comparison with people with prediabetes defined using ADA fasting glucose concentration cutoffs at visit 2, use of ADA HbA_{1c} cutoffs to define prediabetes was more likely to identify people who were women, black, current smokers, had hypertension, and who had less high-school education; it was less likely to identify current drinkers (table 1). In comparison with people defined using ADA fasting glucose concentration cutoffs at visit 4, use of ADA and WHO 2 h glucose concentration to define prediabetes was more likely to identify women, and less

	ADA fasting glucose clinical categories			ADA HbA_{1c} clinical categories		
	Normoglycaemia <5·6 mmol/L (n=6215)	Prediabetes 5·6–6·9 mmol/L (n=4112)	Undiagnosed diabetes ≥7·0 mmol/L (n=517)	Normoglycaemia <5·7% (<39 mmol/mol) (n=8355)	Prediabetes 5·7–6·4% (39–46 mmol/mol) (n=2027)	Undiagnosed diabetes ≥6·5% (≥48 mmol/mol) (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)
Women	3928 (63%)	1967 (48%)	281 (54%)	4794 (57%)	1098 (54%)	284 (61%)
Black	1074 (17%)	1031 (25%)	193 (37%)	1251 (15%)	818 (40%)	230 (50%)
Less than high-school education	1015 (16%)	877 (21%)	145 (28%)	1302 (16%)	586 (29%)	149 (32%)
BMI (kg/m²)	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/m²)	1168 (19%)	1418 (34%)	281 (54%)	1813 (22%)	779 (38%)	275 (60%)
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 concentration (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)
HbA_{1c} (%)	5·34% (0·38)	5·59% (0·44)	6·97% (1·51)	5·29% (0·28)	5·98% (0·17)	7·42% (1·43)
HbA_{1c} (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)
Hypercholesterolaemia	4601 (74%)	3360 (82%)	453 (88%)	6329 (76%)	1679 (83%)	406 (88%)
Hypertension	1522 (24%)	1555 (38%)	282 (55%)	2250 (27%)	860 (42%)	249 (54%)
eGFR (mL/min per 1·73 m²)	97·3 (13)	96·9 (14)	99·7 (15)	96·8 (13)	98·2 (15)	101 (16)
Current smoker	1342 (22%)	888 (22%)	102 (20%)	1657 (20%)	566 (28%)	109 (24%)
Current drinker	3779 (61%)	2433 (59%)	280 (54%)	5286 (63%)	1013 (50%)	193 (42%)
Family history of diabetes	1262 (20%)	1012 (25%)	174 (34%)	1780 (21%)	511 (25%)	157 (34%)

Data are mean (SD) or n (%). ARIC=Atherosclerosis Risk in Communities study. ADA=American Diabetes Association. eGFR=estimated glomerular filtration rate.

Table 1: **Baseline characteristics of ARIC participants (visit 2, 1990–92) without a history of cardiovascular disease or diagnosed diabetes by different definitions of prediabetes**

	ADA fasting glucose clinical categories			ADA and WHO 2 h glucose clinical categories		
	Normoglycaemia <5·6 mmol/L (n=4720)	Prediabetes 5·6–6·9 mmol/L (n=2142)	Undiagnosed diabetes ≥7·0 mmol/L (n=332)	Normoglycaemia <7·8 mmol/L (n=4442)	Prediabetes 7·8–11·0 mmol/L (n=2009)	Undiagnosed diabetes ≥11·0 mmol/L (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)
Women	2983 (63%)	1024 (48%)	172 (52%)	2462 (55%)	1256 (63%)	461 (62%)
Black	682 (14%)	454 (21%)	85 (26%)	759 (17%)	310 (15%)	152 (20%)
Less than high-school education	640 (14%)	390 (18%)	77 (23%)	605 (14%)	341 (17%)	161 (22%)
BMI (kg/m²)	27·4 (5·0)	30·1 (5·3)	32·1 (6·0)	27·7 (5·1)	29·2 (5·3)	30·5 (5·6)
Obese (≥30 kg/m²)	1132 (24%)	966 (45%)	200 (60%)	1162 (26%)	774 (39%)	362 (49%)
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 concentration (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 h glucose concentration (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)
Hypercholesterolaemia	3473 (74%)	1768 (83%)	291 (88%)	3260 (73%)	1628 (81%)	644 (87%)
Hypertension	1703 (36%)	1024 (48%)	201 (61%)	1524 (34%)	962 (48%)	442 (59%)
eGFR (mL/min per 1·73 m²)	88·2 (12)	88·3 (13)	89·6 (12)	88·1 (12)	88·5 (13)	88·7 (13)
Current smoker	660 (14%)	309 (14%)	39 (12%)	693 (16%)	235 (12%)	80 (11%)
Current drinker	2605 (55%)	1184 (55%)	163 (49%)	2567 (58%)	1038 (52%)	347 (47%)
Family history of diabetes	933 (20%)	564 (26%)	110 (33%)	851 (19%)	527 (26%)	229 (31%)

Data are mean (SD) or n (%). ARIC=Atherosclerosis Risk in Communities study. ADA=American Diabetes Association. eGFR=estimated glomerular filtration rate.

Table 2: **Baseline characteristics of ARIC participants (visit 4, 1996–98) without a history of cardiovascular disease or diagnosed diabetes by different definitions of prediabetes**

	Prevalence	95% CI
Visit 2 (1990–92; age range 47–70 years)		
ADA fasting glucose concentration, 5·6–6·9 mmol/L	4112/10 844 (38%)	37·0–38·8
WHO fasting glucose concentration, 6·1–6·9 mmol/L	1213/10 844 (11%)	10·6–11·8
ADA HbA_{1c}, 5·7–6·4% (39–46 mmol/mol)	2027/10 844 (19%)	18·0–19·4
IEC HbA_{1c}, 6·0–6·4% (42–46 mmol/mol)	970/10 844 (9%)	8·4–9·5
Visit 4 (1996–98; age range 53–76 years)		
ADA fasting glucose concentration, 5·6–6·9 mmol/L	2142/7194 (30%)	28·7–30·8
WHO fasting glucose concentration, 6·1–6·9 mmol/L	621/7194 (9%)	8·0–9·3
ADA and WHO 2 h glucose concentration, 7·8–11·0 mmol/L	2009/7194 (28%)	26·9–29·0

ADA=American Diabetes Association. IEC=International Expert Committee.

***Table 3*: Prevalence of prediabetes by definition**

likely to identify black and obese people, but baseline risk factors were otherwise similar (table 2). Characteristics of participants identified as having prediabetes using WHO fasting glucose concentration cutoffs and using IEC HbA_{1c} cutoffs are shown in the appendix.

The prevalence of prediabetes varied between different definitions of prediabetes (table 3). Cross-tabulation of the different definitions are shown in the appendix.

Among 10 844 participants included in the analyses for visit 2, 3152 incident cases of diabetes, 2608 incident cases of chronic kidney disease, 1556 incident atherosclerotic cardiovascular events, 266 incident cases of peripheral arterial disease, and 3177 deaths were reported in approximately 22 years of follow-up. Among 7194 participants included in the analyses for visit 4, 1859 incident cases of diabetes, 1444 incident cases of chronic kidney disease, 760 incident atherosclerotic cardiovascular events, 115 incident cases of peripheral arterial disease, and 1568 deaths were reported in approximately 16 years of follow-up (appendix).

Comparison of the sensitivity and specificity for each definition of prediabetes for 10 year risk of each outcome showed that definitions using ADA and IEC HbA_{1c} cutoffs, and WHO fasting glucose concentration cutoffs had higher specificity than ADA fasting glucose concentration cutoffs for all outcomes, whereas ADA fasting glucose concentration cutoffs, and ADA and WHO 2 h glucose concentration cutoffs, were more sensitive than WHO fasting glucose concentration cutoffs (table 4). ADA and IEC HbA_{1c} cutoffs, and WHO fasting glucose concentration cutoffs had higher positive predictive values and negative likelihood ratios for incident diabetes and higher positive likelihood ratios for all outcomes compared with ADA fasting glucose concentration cutoffs. Negative predictive values were numerically similar across outcomes.

In Cox proportional hazard models for age, sex, and, race centre, prediabetes by all five definitions was significantly associated with risk of future clinical outcomes (table 5). In participants identified as having prediabetes using HbA_{1c}-based definitions, incidence rates were higher, hazard ratios were larger, and C-statistics for chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality were higher, than in participants identified using ADA and WHO fasting glucose concentration cutoffs (table 5; appendix). Adjusting for additional risk factors did not alter our findings (appendix). The differences in the C-statistics between HbA_{1c}-based definitions and glucose-based definitions, although statistically significant, were small (improvement in the C-statistic was generally less than 0·02). Prediabetes defined using ADA HbA_{1c} cutoffs also showed significant overall improvement in the cNRI for atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality compared to prediabetes defined using ADA and WHO fasting glucose concentration cutoffs (appendix). 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 HbA_{1c}-based definitions than the ADA fasting glucose concentration-based definition.

For incident diabetes, after demographic adjustment, IEC HbA_{1c} cutoffs had the largest hazard ratio, but the ADA fasting glucose concentration cutoffs had a significantly higher C-statistic and better classified people at risk for future incident diabetes based on overall cNRI improvement (table 5; appendix). However, after adjustment for additional risk factors (fully adjusted model), no significant difference in the C-statistics for ADA fasting glucose clinical categories compared with the other definitions remained (appendix).

The hazard ratios and C-statistics for all outcomes were similar when all ADA and WHO glucose prediabetes definitions were compared, with the exception of incident diabetes. Although the hazard ratio for WHO fasting glucose-defined prediabetes was higher, the C-statistic for ADA fasting glucose-defined prediabetes was modestly, although significantly, improved for classification of people at risk of developing diabetes (table 5; appendix). However, these differences did not persist after adjustment for additional risk factors (fully adjusted model).

Exclusion of people with undiagnosed diabetes did not alter our findings (appendix). We did not observe consistent differences in results across outcomes in analyses by race, with the exception of incident diabetes which was significantly different between black and white people (appendix). Across all definitions, black people were less likely to report a subsequent diagnosis of diabetes or glucose-lowering-medication use during follow-up than were white people in the demographic adjusted model (all $p_{interaction}<0·05$; appendix). After adjustment for additional risk factors (fully adjusted model) the difference between black people and white people was reduced, although the interaction for some definitions (WHO fasting glucose concentration, IEC HbA_{1c}, ADA HbA_{1c}, and ADA and WHO 2 h glucose concentration) remained statistically significant (appendix). In analyses stratified by sex, a stronger association existed between prediabetes and

	Visit 2 (1990–92)				Visit 4 (1996–98)		
	ADA fasting glucose concentration 5·6–6·9 mmol/L	WHO fasting glucose concentration 6·1–6·9 mmol/L	ADA HbA_{1c} 5·7–6·4% (39–46 mmol/mol)	IEC HbA_{1c} 6·0–6·4% (42–46 mmol/mol)	ADA fasting glucose concentration 5·6–6·9 mmol/L	WHO fasting glucose concentration 6·1–6·9 mmol/L	ADA and WHO 2 h glucose concentration 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)
Positive predictive value	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)
Negative predictive value	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)
Positive likelihood ratio	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)
Negative likelihood ratio	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)
Positive predictive value	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)
Negative predictive value	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)
Positive likelihood ratio	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)
Negative likelihood ratio	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)
Positive predictive value	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)
Negative predictive value	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)
Positive likelihood ratio	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)
Negative likelihood ratio	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)
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)
Positive predictive value	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)
Negative predictive value	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)
Positive likelihood ratio	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)
Negative likelihood ratio	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)
Positive predictive value	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)
Negative predictive value	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)
Positive likelihood ratio	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)
Negative likelihood ratio	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)

Data are proportion (95% CI) or ratio (95% CI). ADA=American Diabetes Association. IEC=International Expert Committee.

***Table 4*: 10 year sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of incident clinical outcomes according to different definitions of prediabetes versus normoglycaemia at baseline**

undiagnosed diabetes with peripheral arterial disease in women than in men for both HbA_{1c}-based and fasting glucose-based definitions (appendix). By contrast, ADA and WHO 2 h glucose was not significantly associated with incident peripheral arterial disease in men or women. Mortality associations, regardless of definition, were also stronger in women than in men.

Our ancillary analysis in NHANES III (appendix) showed 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 prediabetes identified using IEC HbA_{1c} cutoffs were the largest, followed by ADA fasting glucose concentration cutoffs, ADA HbA_{1c} cutoffs, ADA and WHO 2 h glucose concentration cutoffs, and WHO fasting glucose concentration cutoffs (appendix).

Discussion

In this cohort study, we showed that prevalence of prediabetes and performance of various definitions of prediabetes were significantly different when analysed in

	Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
Visit 2 (1990–92; age range 47–70 years)					
ADA fasting glucose concentration					
<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 concentration					
<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 HbA_{1c} concentration					
<5·7% (<39 mmol/mol)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5·7–6·4% 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)*
≥6·5% (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 HbA_{1c} concentration					
<6·0% (<42 mmol/mol)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
6·0–6·4% (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)*
≥6·5% (≥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; age range 53–76 years)					
ADA fasting glucose concentration					
<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 concentration					
<6·1 mmol/L	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
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 and WHO 2 h glucose concentration					
<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)

Data are HR (95% CI) or C-statistic (95% CI), unless otherwise specified. Adjusted for age, sex (male, female), race centre (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC). ADA=American Diabetes Association. IEC=International Expert Committee. HR=hazard ratio. *p<0·05. †Undiagnosed diabetes.

***Table 5*: Demographic adjusted hazard ratio and Harrell's C-statistic for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes**

the context of long-term complications. Use of ADA fasting glucose concentration cutoffs or ADA and WHO 2 h glucose concentration cutoffs to define prediabetes resulted in higher prevalence estimates than did use of WHO fasting glucose concentration cutoffs, ADA HbA_{1c} cutoffs, or IEC HbA_{1c} cutoffs. With the ADA fasting glucose concentration definition, over a third of the study population was estimated to have prediabetes. ADA HbA_{1c} cutoffs, IEC HbA_{1c} cutoffs, and WHO fasting glucose concentration cutoffs were the most specific definitions for identification of people at risk for long-term clinical outcomes, resulting in higher positive likelihood ratios than the other definitions, whereas ADA fasting glucose concentration cutoffs and ADA and WHO 2 h glucose concentration cutoffs were more sensitive than ADA and IEC HbA_{1c} cutoffs, and WHO fasting glucose concentration cutoffs. These differences in sensitivity and specificity are important for choosing a definition of prediabetes for use in a screening programme.

Differences in risk discrimination across prediabetes definitions were modest, but clinical categories for prediabetes based on HbA_{1c} (ADA or IEC) definitions

performed slightly better than those based on fasting glucose concentrations for microvascular and macrovascular outcomes. Net reclassification improvement also supported prediabetes defined by ADA HbA_{1c} cutoffs as a better classifier for people at risk of future cardiovascular and mortality outcomes. In minimally adjusted models, fasting glucose-defined prediabetes was slightly better for prediction of future diabetes than HbA_{1c}-defined prediabetes. This result is not surprising because most cases of diabetes would have been identified by a healthcare provider during follow-up on the basis of elevations in glucose concentrations since HbA_{1c} was not recommended for use in diagnosis until 2009. Clinical categories defined using ADA fasting glucose concentration, WHO fasting glucose concentration, and ADA and WHO 2 h glucose concentration were generally similar for risk discrimination of clinical outcomes.

Across all definitions of prediabetes, whether defined using fasting glucose concentration, HbA_{1c}, or 2 h glucose concentration, black people were less likely to report a diagnosis of diabetes or diabetes medication use during follow-up. This suggests that for the same level of hyperglycaemia, black people might be more likely to have delays in diagnosis, reflecting disparities in socioeconomic status 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. One ARIC study[22] found that fasting glucose concentration of 5·6–6·9 mmol/L and 2 h glucose of 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. Our results confirm these findings, but with approximately 10 more years of follow-up and more incident events. Our findings are also consistent with results from the Emerging Risk Factors Collaboration (ERFC),[23] a 73-study, participant-level meta-analysis of 294 998 individuals. The ERFC study found that, compared with fasting glucose, random glucose, or postload glucose, HbA_{1c} provided a small, but significant, improvement in the C-statistic for discrimination of cardiovascular disease risk.

By contrast, in the 2001 DECODE study[24] of 22 514 participants from ten different European centres followed up for 8·8 years, 2 h glucose was more strongly associated with atherosclerotic cardiovascular death and all-cause mortality than was fasting glucose concentration. We do note that measurements in different blood specimens (plasma, whole blood) were collected in DECODE across the ten European centres. Methodological and study population differences notwithstanding, the reasons why our results do not agree with the DECODE findings are unclear. Meta-analyses[25,26] have also shown conflicting results for whether impaired fasting glucose or impaired glucose tolerance is more strongly associated with cardiovascular disease outcomes.

Several limitations of our study should be considered in the interpretation of our findings. First, we did not have concurrent measurements of fasting glucose, HbA_{1c}, and 2 h glucose, and all classifications were based on single measurements whereas in clinical practice, these measurements might be repeated. In practice, clinical decisions are based on a compendium of laboratory, clinical, and epidemiological information. Nonetheless, for prediabetes, there are currently no formal recommendations or consensus regarding repeating tests for confirmation. Second, as part of the ARIC study protocol, abnormal laboratory values including raised fasting glucose concentration (>11·1 mmol/L) or 2 h glucose (>16·7 mmol/L) were reported back to the participants, although less than 1·5% of participants had elevated values that prompted a report. HbA_{1c} results at visit 2 were not reported to participants as they were measured retrospectively (>10 years after sample collection). The reporting of the glucose measures to participants might have increased the probability of a diagnosis of diabetes.[27] Third, we used a definition of incident diabetes based on self-report. Fourth, our findings might not be generalisable beyond black and white Americans. Fifth, despite the large sample size and number of events, the possibility exists that the study might have been underpowered to detect moderate differences between definitions, particularly given the overlap of definitions. Finally, although our results in ARIC were consistent with findings for all-cause and cardiovascular mortality in NHANES III, further replication, especially for other major complications in diverse populations, is needed. The strengths of this study include our ability to compare the prognostic value of multiple definitions of prediabetes, rigorous assessment of hyperglycaemia and related risk factors with standardised protocols and trained personnel, active surveillance for major clinical complications, and over two decades of follow-up in a large, community-based population.

A number of considerations need to be weighed when deciding between definitions of prediabetes for screening programmes, and the optimal choice will depend on 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 establish whether a strategy that would identify large numbers of people, including many people at low risk of future outcomes, might be more beneficial than strategies that are highly specific, but might miss some high-risk individuals who should receive preventive interventions. Prediabetes defined by ADA and IEC HbA_{1c} cutoffs, and WHO fasting glucose concentration cutoffs identified fewer people, but these definitions were more specific for the identification of people at risk for long-term outcomes. HbA_{1c}-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 prediabetes defined by ADA fasting glucose concentration cutoffs was more sensitive, it was not as strongly associated with long-term risk of clinical complications. For long-term prediction of clinical outcomes, prediabetes definitions based on 2 h glucose concentration did not better predict the risk of chronic kidney disease or cardiovascular outcomes than fasting glucose concentration. The comparative usefulness of different definitions of prediabetes will vary depending on the goals of the screening programme; however, data on long-term prognostic performance can, and should, help to inform use of and recommendations for different definitions of prediabetes.

Contributors

BW and ES designed the study and drafted the report. BW and NRD analysed the data. All authors made meaningful revisions to the manuscript.

Declaration of interests

JSP received grants from the US National Institutes of Health (NIH) unrelated to this work. KM received grants from the NIH and the US National Kidney Foundation unrelated to this work, as well as grants and personal fees from Kyowa Hakko Kirin and Fukuda Denshi and personal fees from Sumitomo Dainippon Pharma, unrelated to this work. NMP has received grants from Philips Respironics and Resmed, unrelated to this work. MW has received personal fees from Amgen, unrelated to this work. ES received grants from the NIH National Institute of Diabetes and Digestive and Kidney Diseases for this study, as well as grants from the NIH and the Foundation for the NIH, unrelated to this work. BW, NRD, and MG declare no competing interests.

Acknowledgments

The Atherosclerosis Risk in Communities Study is a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) (contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). BW was supported by National Institutes of Health (NIH)/NHLBI grant T32HL007024. This research was supported by NIH/National Institute of Diabetes and Digestive and Kidney Diseases grants R01DK089174 and K24DK106414, awarded to ES. We thank the staff and participants of the ARIC study for their important contributions.

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