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Original Contribution

Strength of Association for Incident Diabetes Risk Factors According to Diabetes Case Definitions

The Atherosclerosis Risk in Communities Study

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Prospective epidemiologic studies have characterized major risk factors for incident diabetes by a variety of diabetes case definitions. Whether different definitions alter the association of diabetes with risk factors is largely unknown. Using 1987–1998 data from the ongoing Atherosclerosis Risk in Communities (ARIC) Study, the authors assessed the relation of traditional risk factors with 3 different diabetes case definitions and 4 fasting glucose categories. They compared the study protocol case definition with 2 nested case definitions, self-reported diabetes and a multiple-evidence definition. Significant differences in risk factor associations by case definition and by screening cutpoints were observed. Specifically, the magnitude of the association between the risk factors (baseline metabolic syndrome, fasting glucose, blood pressure, body mass index, and serum insulin) and incident diabetes differed by case definition. Associations with these risk factors were weaker with a case definition based on self-report compared with other definitions. These results illustrate the potential limitations of case definitions that rely solely on self-report or those that incorporate measured glucose values to ascertain undiagnosed cases. Although the ability to identify risk factors of diabetes was consistent for the case definitions studied, tests of novel risk factors may result in different estimates of effect sizes depending on the definition used.

diabetes mellitus, type 2; epidemiologic methods

Abbreviations: ARIC, Atherosclerosis Risk in Communities; HbA1c, glycosylated hemoglobin; IRR, incidence rate ratio; NHANES, National Health and Nutrition Examination Survey.

Multiple prospective epidemiologic studies have characterized major risk factors for incident diabetes. These studies have used a variety of criteria to define diabetes incidence including self-report, medication use, fasting or nonfasting glucose levels, and/or results from an oral glucose tolerance test. Of these, the oral glucose tolerance test is less common as it is difficult to implement in large studies, burdensome on the participants, and not routinely used to diagnose diabetes in the United States.

Three large, well-characterized studies—the Iowa Women's Health Study (1), the First National Health and Nutrition Examination Survey (NHANES) (2), and the Nurses' Health Study (3)—used self-report as the only criterion to identify incident cases of diabetes. Using NHANES data from 5 consecutive examinations (1960–2000), Gregg et al. (4) observed large increases in diagnosed diabetes in the overweight and obese, indicating potential diagnostic suspicion bias for obese individuals. In general, any individual characteristic that is associated with more frequent glucose screening or medical surveillance could bias the relation of diabetes with risk factors. If the case definition affects the magnitude and/or direction of associations between risk factors, such differences could be important in our understanding of the epidemiology of diabetes. Whether different case definitions alter the associations of diabetes with risk factors is largely unknown. We addressed this knowledge gap in the Atherosclerosis

Risk in Communities (ARIC) Study by assessing the relation of traditional risk factors with 3 different diabetes case definitions and 4 fasting glucose categories.

MATERIALS AND METHODS

Subjects

The ARIC Study is an ongoing prospective cohort study originally designed to investigate risk factors of subclinical and clinical atherosclerosis, and it included rigorous measurements of cardiovascular and diabetes risk factors. ARIC Study investigators enrolled 15,792 participants, aged 45–64 years, from 4 field centers: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The ARIC Study has been described in detail elsewhere (5). We analyzed data from the baseline examination in 1987–1989 and 3 triennial follow-up visits for a maximum of 9 years of follow-up for incident type 2 diabetes, as incident type 1 diabetes is unlikely in this middle-aged cohort. For the present analysis, we excluded persons on the basis of the following criteria: race other than black or white ($n = 48$), blacks from centers with small numbers ($n = 55$), missing baseline diabetes status ($n = 147$), prevalent diabetes at baseline using the ARIC Study protocol case definition ($n = 1{,}863$), and missing data to assess incident diabetes at all follow-up visits ($n = 879$). The final analysis sample included 12,800 individuals without type 1 or type 2 diabetes at baseline and with a mean follow-time of 7.6 years.

Measurements

The risk factors examined in these analyses were ascertained at visit 1 (baseline), as described in detail in the ARIC Study manuals of operation (5). Serum glucose was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method, fasting serum insulin by nonspecific radioimmunoassay, and triglycerides and high density lipoprotein cholesterol by enzymatic methods. Individuals who had a parent with diabetes were taken to have a positive family history of diabetes. Body mass index was calculated as weight (kg)/height $(m)^2$. Hip and waist circumferences were measured at the maximal protrusion of the hips and at the level of the umbilicus with the participant standing erect. Metabolic syndrome was defined as having 3 or more of the following factors: blood pressure $\geq$130/85 mm Hg, fasting glucose $\geq$100 mg/dL, large waist circumference (men: $\geq$102 cm, women: $\geq$88 cm), a low level of high density lipoprotein cholesterol (men: $<$40 mg/dL, women: $<$50 mg/dL), or triglycerides $\geq$150 mg/dL (6). Medical and personal histories were ascertained via interview. Annual telephone follow-up maintained contact and assessed the health status of the participants.

Incident diabetes case definitions and fasting glucose categories

For this study, we compared 3 case definitions to define incident diabetes—the ARIC Study protocol case definition and 2 nested case definitions, self-reported physician's diagnosis and a multiple-evidence definition (Table 1). The multiple-evidence case definition is the most stringent and includes those subjects with a minimum of 2 of the ARIC Study criteria, making it more specific but less sensitive. Self-reported diabetes was defined as a positive response to the question, ''Has a doctor ever said you had diabetes or sugar in the blood?'' The ARIC Study definition was used to determine prevalent diabetes. Additionally, we compared 4 fasting glucose screening categories: 126–129, 130–134, 135–139, and $\geq$140 mg/dL.

Table 1. Incident Case Definitions, Atherosclerosis Risk in Communities Study, 1987–1998

Case Definition	Criteria
ARIC Study	Self-reported a physician's diagnosis of diabetes or
	Reported use of diabetes medication in the past 2 weeks or
	Had a fasting ($\geq$8 hours) glucose measurement of $\geq$126 mg/dL or a nonfasting glucose measurement of $\geq$200 mg/dL
Self-report	Self-reported a physician's diagnosis of diabetes
Multiple evidence	Subjects with 2 of the ARIC Study criteria listed above

Abbreviation: ARIC, Atherosclerosis Risk in Communities.

Statistical analysis

The date of diabetes incidence was estimated by linear interpolation using glucose values at the ascertaining visit and the previous one, as previously described (7). Multivariable analyses were performed to estimate associations of risk factors with different case definitions of diabetes. To formally compare these associations across case definitions while accounting for the lack of independence between the definition-specific results, we used a hierarchical approach. Incident diabetes by each case definition was treated as a separate event, and these events, nested within each participant, were analyzed within 1 model. Generalized linear models using a Poisson distribution, a log-link, and log (time to event) as an offset and assuming an unstructured covariance matrix between events were used to estimate the association (incidence rate ratio) and test for statistical significance of the variation in these incidence rate ratios among the 3 case definitions. Generalized linear models were fit and tested by using the generalized estimating equation method (8) (PROC GENMOD; SAS Institute, Inc., Cary, North Carolina). These results were qualitatively confirmed by using a parallel hierarchical method with 3 (time-to-event/event) outcomes for each subject, Cox proportional hazard regression, and use of the generalized estimating equation approach implemented with the COVSANDWICH option in PHREG (SAS Institute, Inc.). The null hypothesis that baseline characteristics are the same across 4 fasting glucose categories was tested by a simple linear correlation between the glucose category and continuous variables or by the Armitage trend test in the case of binary variables. Models were adjusted for age, race, and sex.

Table 2. Characteristics Among Adult Subjects Without Diabetes at Baseline (1987–1989) and Incident Diabetes by Case, Atherosclerosis Risk in Communities Study

Baseline Characteristics	Full Cohort (n = 12,800)			Incident Diabetes Case Definition[a]								
				ARIC Study (n = 1,441)			Self-Report (n = 293)			Multiple Evidence (n = 186)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Total incident cases												
Visit 2 (1990–1992)				741			128			82		
Visit 3 (1993–1995)				394			78			53		
Visit 4 (1996–1998)				306			87			51		
Male		44			50			46			49	
Black race		23			33			32			37	
Age, years			54 (5.7)			54 (5.6)			54 (5.2)			54 (5.7)
High school graduate		80			72			70			69	
Body mass index[b]			27 (5)			30 (5.6)			30 (5.4)			31 (5.2)
Waist/hip ratio			0.919 (0.08)			0.959 (0.07)			0.957 (0.07)			0.966 (0.06)
Metabolic syndrome, yes		30			62			54			62	
Blood glucose, mg/dL			99 (9)			108 (9)			105 (10)			107 (10)
Insulin, pmol/L			77 (59)			119 (77)			117 (81)			133 (90)
Parental history of diabetes, yes		22			33			38			38	
Systolic blood pressure, mm Hg			120 (18)			126 (18)			123 (16)			125 (16)
Diastolic blood pressure, mm Hg			73 (11)			76 (11)			75 (10)			77 (10)
Hypertension medication use		27			42			43			47	
HDL cholesterol, mg/dL			53 (17)			46 (14)			47 (14)			45 (14)
Triglycerides, mg/dL			124 (77)			154 (99)			156 (134)			168 (154)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; HDL, high density lipoprotein; SD, standard deviation.

[a] ARIC Study: self-reported a physician's diagnosis of diabetes, reported diabetes medication use, or had a fasting glucose measurement of $\geq$126 mg/dL or a nonfasting glucose measurement of $\geq$200 mg/dL; self-reported: self-reported a physician's diagnosis of diabetes; multiple evidence: a minimum of 2 of the ARIC Study criteria listed above.

[b] Body mass index measured as weight (kg)/height (m)^2.

RESULTS

Using the ARIC Study protocol case definition of diabetes, we found that there were 1,441 incident cases of diabetes over 9 years of follow-up out of 12,800 subjects who were free of diabetes at baseline. Of the 1,441 cases determined by the ARIC Study definition, 78% (n = 1,126) of cases were initially detected solely by a fasting glucose measurement of $\geq$126 mg/dL, and 20% (n = 293) self-reported diabetes status with or without the other criteria having been met. Of the remaining 2% (n = 22), 21 were currently taking diabetes medication but did not self-report diabetes, and 1 had a nonfasting glucose measurement of >200 mg/dL. Of the incident diabetes cases who self-reported diabetes (n = 293), self-report was the sole criterion for 38% (n = 112) with the other 62% (n = 181) of subjects having met an additional criterion (i.e., high fasting glucose or diabetes medication use). Of the 1,441 incident diabetes cases, 186 were included in our multiple-evidence case definition with at least 2 of the 3 ARIC Study criteria being met: high fasting glucose, self-reported physician's diagnosis, or medication use.

Table 2 shows baseline characteristics of the full cohort and all incident cases of diabetes as defined by the ARIC Study case definition. In addition, 2 nested case definitions of the ARIC Study-defined incident cases are shown, self-report and multiple evidence. Irrespective of the case definition used, subjects who had incident diabetes during follow-up had a worse baseline risk factor profile than that of the overall study population. At baseline, these subjects had greater adiposity, as indicated by a higher mean body mass index and waist/hip ratio; higher mean levels of fasting glucose, insulin, triglycerides, and blood pressure; and lower mean levels of high density lipoprotein cholesterol. In addition, they were more likely to have metabolic syndrome, to use hypertension medication, and to have a positive family history of diabetes.

Incidence rate ratios for the 3 case definition groups and major diabetes risk factors are listed in Table 3. Significant differences between incidence rate ratios for the case definition groups were observed for metabolic syndrome, fasting glucose, systolic and diastolic blood pressure, body mass index, fasting insulin, and triglycerides. For metabolic

Table 3. Incidence Rate Ratios for Incident Diabetes by Diagnostic Criteria Among Adults Free of Diabetes at Baseline (1987–1989), Atherosclerosis Risk in Communities Study[a]

Categorical Risk Factors	Incident Diabetes Case Definition[b]			*P* Value
	ARIC Study (*n* = 1,441)	Self-Report (*n* = 293)	Multiple Evidence (*n* = 186)	
Absolute cumulative incidence at 9 years[c]	0.123	0.027	0.017	
Gender				
Female	1.0	1.0	1.0	
Male	1.3	1.1	1.3	0.19
Race				
White	1.0	1.0	1.0	
Black	2.0	1.9	2.4	0.06
High school graduate				
No	1.0	1.0	1.0	
Yes	0.72	0.63	0.62	0.54
Waist/hip ratio				
Tertile 1 (<0.89)	1.0	1.0	1.0	
Tertile 2 (0.89–0.95)	2.6	2.1	2.9	0.79
Tertile 3 (≥0.96)	5.7	4.9	6.9	0.37
Metabolic syndrome				
No	1.0	1.0	1.0	
Yes	4.4	3.2	4.5	<0.001
Baseline fasting glucose, mg/dL				
<100	1.0	1.0	1.0	
100–125	6.1	3.4	4.3	<0.001
Parental history of diabetes				
No	1.0	1.0	1.0	
Yes	1.8	2.2	2.2	0.15
Continuous risk factors (per standard deviation)				
Age (6 years)	1.1	1.1	1.0	0.79
Systolic blood pressure (19 mm Hg)	1.37	1.18	1.30	<0.001
Diastolic blood pressure (11 mm Hg)	1.24	1.10	1.23	<0.001
Body mass index (5 kg/m^2)	1.64	1.57	1.69	0.002
HDL cholesterol (7 mg/dL)	0.53	0.57	0.48	0.10
Log of insulin (0.77 pmol/L)	2.47	2.32	2.96	<0.001
Log of triglycerides (0.52 mg/dL)	1.64	1.60	1.88	0.007

Abbreviations: ARIC, Atherosclerosis Risk in Communities; HDL, high density lipoprotein.

[a] Gender, age, and race models are adjusted for each other; other phenotypes are all adjusted for age, race, and gender.

[b] ARIC Study: self-reported a physician's diagnosis of diabetes, reported diabetes medication use, or had a fasting glucose measurement of ≥126 mg/dL or a nonfasting glucose measurement of ≥200 mg/dL; self-reported: self-reported a physician's diagnosis of diabetes; multiple evidence: a minimum of 2 of the ARIC Study criteria listed above.

[c] Cumulative incidence at 9 years was computed by using the Kaplan-Meier estimator.

syndrome, the incidence rate ratio (IRR) was lower in the self-report group (IRR = 3.2) compared with those of the ARIC Study (IRR = 4.4) or multiple-evidence (IRR = 4.5) groups. For baseline fasting glucose, the strength of association was graded across the groups with the highest rate ratio observed in the ARIC Study group (IRR = 6.1), followed by the multiple-evidence group (IRR = 4.3), and then the self-report group (IRR = 3.4). A similar pattern was observed for systolic and diastolic blood pressure. For insulin, body mass index, and triglycerides, the associations were strongest in the multiple-evidence group and weakest in the self-report group.

To investigate the relation between risk factors and fasting glucose-screening categories, we compared baseline (visit 1) levels of risk factors with visit 2 incident cases (Table 4). Significant differences were observed for baseline body mass

Table 4. Characteristics of Visit 2 (1990–1992) Incident Diabetes Detected by Fasting Glucose Alone Among Adults Free of Diabetes at the Baseline Examination (1987–1989), Atherosclerosis Risk in Communities Study

	Fasting Glucose Screening Categories at Visit 2								*P* Value
	126–129 mg/dL (n = 186)		130–134 mg/dL (n = 131)		135–139 mg/dL (n = 82)		≥140 mg/dL (n = 203)		
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	
Male	50		54		56		42		0.12
Age, years		55 (6)		54 (6)		54 (6)		54 (6)	0.20
Black race	35		37		29		42		0.24
High school graduate, yes	70		70		74		72		0.65
Body mass index[a]		30 (4.9)		29.6 (5.1)		29.7 (4.8)		32.2 (6.3)	<0.001
Waist/hip ratio		0.96 (0.06)		0.95 (0.07)		0.97 (0.06)		0.97 (0.07)	0.01
Metabolic syndrome, yes	65		58		71		71		0.07
Systolic blood pressure, mm Hg		127 (18)		126 (18)		125 (16)		129 (20)	0.61
Diastolic blood pressure, mm Hg		75 (10)		77 (12)		78 (10)		78 (12)	0.05
Blood glucose, mg/dL		110 (8)		111 (9)		111 (8)		112 (9)	0.007
Insulin, pmol/L		109 (59)		112 (66)		119 (80)		135 (75)	<0.001
HDL cholesterol, mg/dL		46 (13)		48 (14)		44 (14)		45 (13)	0.28
Triglycerides, mg/dL		143 (77)		146 (102)		169 (108)		154 (80)	0.06
Parental history of diabetes, yes	36		33		30		35		0.90
Diabetes diagnosis conflicted at a subsequent visit	63		46		37		17		<0.001

Abbreviations: HDL, high density lipoprotein; SD, standard deviation.
[a] Body mass index measured as weight (kg)/height $(m)^2$.

index and insulin, with higher levels observed in subjects identified above the highest fasting glucose category (≥140 mg/dL) compared with those identified with lower categories (126–139 mg/dL). The percentage of subjects whose diabetes status was unconfirmed at visit 3 or 4 decreased considerably at higher fasting glucose cutoffs.

To further investigate the extent to which incident cases are confirmed in subsequent visits, we compared incident cases from visit 2 who self-reported diabetes status ($n = 128$) with those whose diabetes status was determined solely from elevated fasting glucose at visit 2 ($n = 603$). We excluded 10 incident cases that did not fit in 1 of these 2 categories. Figure 1 illustrates the status of these cases at visit 3. For those who self-reported diabetes status at visit 2, 62% were considered diabetic, 19% were not considered diabetic, and 19% were lost to follow-up at visit 3. For those who were detected solely by an elevated fasting glucose level at visit 2, 52% were considered diabetic, 36% were not considered diabetic, and 12% were lost to follow-up at visit 3.

DISCUSSION

The ARIC Study is a large, community-based, longitudinal cohort well-suited for investigating the possible effect of applying different case definitions for incident diabetes in epidemiologic studies. The major study findings include statistically significant differences in risk factor associations by case definition and by fasting glucose screening cutpoints. The findings illustrate the potential limitations of case definitions that rely solely on self-report, as well as definitions that incorporate measured glucose values to ascertain undiagnosed cases.

The magnitude of the association of metabolic syndrome, fasting glucose, blood pressure, body mass index, and insulin on diabetes differed by case definition. In every case, the associations were weaker with self-report compared with the ARIC Study and multiple-evidence definitions. However, these differences for fasting glucose level are mostly a function of the case definitions that include fasting levels, as is the case for the ARIC Study and multiple-evidence case definitions. With the exceptions of glucose and blood pressure, the highest point estimates were observed for the multiple-evidence group, which should have the highest specificity (i.e., least number of false positives). Given this pattern, tests of novel risk factors in studies defining diabetes with self-report may result in false negative findings, a smaller number of events, and thus less precision. However, it is important to note that, although the magnitude of the association was attenuated in the self-report group compared with the others, the direction of the risk factor associations was consistent across case definition groups. Therefore, all 3 case definitions studied would be adequate to detect associations with major risk factors. However, the choice of definitions used could matter when evaluating new or novel risk factors that have weaker effects, as differences in the strength of association between definitions could mean the difference between statistical significance in 1 study versus no significance in another for studies of similar size. As one would expect, case definitions that included a fasting glucose criterion were more

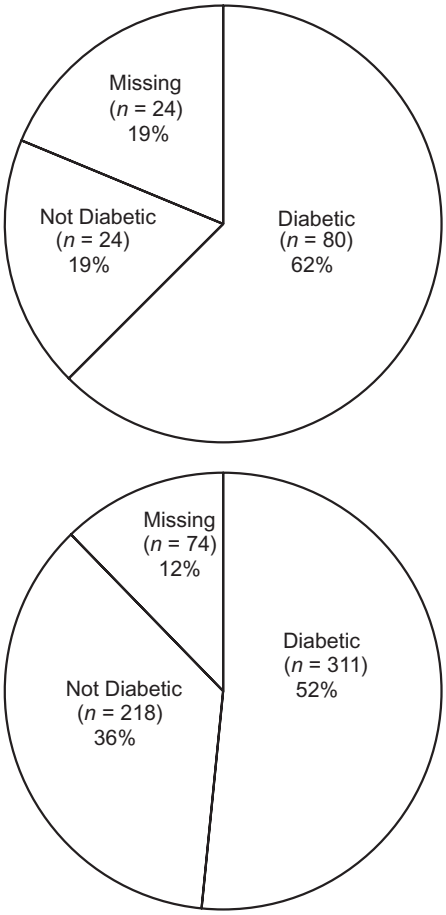

Figure 1. Visit 3 (1993–1995) status of those subjects with incident diabetes at visit 2 (1990–1992) defined by self-reported, physician-diagnosed diabetes (top) or by a fasting glucose measurement of ≥126 mg/dL among adults (bottom) who were free of diabetes at the baseline examination (1987–1989), Atherosclerosis Risk in Communities Study.

strongly associated with baseline fasting glucose compared with self-report.

None of the observed differences in risk by case definition suggests the presence of diagnostic suspicion bias. If diagnostic suspicion bias were present, one would expect subjects with adverse risk factor profiles to be preferentially diagnosed in clinical care, thereby resulting in a higher incidence rate ratio in the self-report group. Without exception, the point estimate for each risk factor that differed by case definition was lowest in the self-report group. Our finding conflicts with observations from NHANES that reported secular trends in diagnosed diabetes in the overweight and obese (9). One possible explanation for the disparate results is that ARIC Study subjects are older, and the last visit was in 1998, which means that increased surveillance would have had to occur prior to the last visit (i.e., early-mid 1990s). Although the NHANES used data from an overlapping time period (1960–2000), their ability to capture clinical practice changes in diabetes screening throughout the 1990s could be responsible for the observed findings. Furthermore, a previous ARIC Study observed that greater adiposity was strongly associated with initial delay in diabetes diagnosis (10).

Significant differences were observed across the 4 fasting-glucose screening cutpoints and baseline risk factor levels. Those who were classified as incident diabetic at visit 2 because of a fasting glucose measurement of ≥140 had a more severe risk factor profile at baseline compared with those classified with lower cutoff levels. A higher proportion of subjects at lower glucose categories were unconfirmed at later visits (i.e., incident visit 2 cases who did not meet the criteria for diabetes in visit 3). This pattern suggests that greater misclassification of disease status, presumably reflecting more false positive results, may have occurred in the lower categories. An additional problem of fasting glucose is that it relies on self-reported fasting status that may be inaccurate for some people and contribute to misclassification.

Reliance on a self-report-only case definition excludes the large population of undetected diabetes cases in the population. Using the ARIC Study definition, 34% of the baseline diabetes cases were identified via a single fasting glucose measurement only. Fasting glucose-detected diabetes remained the predominant single criterion for incident diabetes diagnosis in all subsequent visits: 81%, 79%, and 69% of cases for visits 2, 3, and 4, respectively. One reason for this is because the fasting glucose cutpoint of 140 mg/dL was used clinically until 1997, near the end of ARIC Study visit 4, when it was lowered to 126 mg/dL (11). This means that the percentage of "undiagnosed" cases using the 126-mg/dL cutpoint would likely be lower now than in the timeframe studied. However, the short-term variability in a single glucose measurement poses important issues for the use of glucose screening alone to define diabetes cases and to research how study glucose screening differs from a clinical diagnostic assessment.

Classification of diabetes based on a single fasting glucose measure may be subject to regression to the mean. Indeed, of the incident cases defined solely by fasting glucose for which there are follow-up data, 40% of visit 2 and 28% of visit 3 cases did not meet the standard ARIC Study case definition at a subsequent visit. The 2009 International Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recently recommended that glycosylated hemoglobin (HbA1c) measurements ≥6.5% be used for the diagnosis of diabetes, as opposed to fasting glucose measurements (12). An accurate measurement of HbA1c does not require fasting and, thus, eliminates misclassification due to inaccurate fasting status and reduces patient burden. Furthermore, HbA1c measurements are less variable between and within subjects (13), thus reducing misclassification due to measurement noise. The implications of this new recommendation will need to be evaluated further in epidemiologic studies; however, the improved sensitivity and specificity afforded by HbA1c may make this the future measure of choice in epidemiologic studies.

In conclusion, the magnitude of risk factor associations with incident diabetes differs by diabetes case definition and fasting glucose cutpoints. Associations with traditional risk factors were weaker with a self-report case definition

compared with other case definitions, and the short-term variability of a single glucose measure is problematic. Although the ability to identify risk factors of diabetes was consistent for the case definitions studied, tests of novel risk factors may result in different estimates of effect sizes depending on the case definition used.

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