Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.

Online Supplemental Material: Comparison of Self-reported to Verified Diabetes in the Atherosclerosis Risk in Communities (ARIC) Study

Although self-reported diabetes is highly specific and widely used in epidemiologic studies, its limited sensitivity creates the possibility for misclassification. During long-term (years 7-15 of follow-up) of the Atherosclerosis Risk in Communities (ARIC) Study participants, we only have access to self-reported data from annual telephone calls. During the first 6 years of follow-up (from Visit 2 to Visit 4), however, we have data on blood glucose, recorded medication bottles at each clinic visit, and self-reported history of a physician diagnosis of diabetes. This combination is a highly sensitive case definition and is typically thought to yield nearly complete case ascertainment. This information also affords the opportunity to compare varying definitions of incident diabetes during the first 6 years of follow-up.

The table below compares our results obtained using three different definitions of diabetes after excluding individuals with glucose-lowering medication use or a self-reported diagnosis of diabetes at baseline, unless otherwise noted:

1) Medication Use: 6-year incident diabetes based on diabetes medication use (N=398)

2) Glucose: 6-year incident diabetes based on elevated fasting glucose levels (≥126 mg/dl), (N=127, after additionally excluding individuals with fasting glucose ≥126 mg/dl at baseline)

3) Self-reported diagnosis: 6-year incident diabetes based on self-reported physician diagnosis (N=519)

When comparing the association of baseline glycated hemoglobin with incident diabetes case definitions based on medication use, fasting glucose, or self-reported diagnoses our results were similar (Online Table 1).

Online Table 1. Adjusted Hazard Ratios of Incident Diabetes Comparing Different Diabetes Definitions During the First 6 years of Follow-up

HbA1c Categories	Model 1a	Model 2a	Model 3a
Medication Use: 6-year incident diabetes based on diabetes medication use (N=398 cases)			
<5%	0.43 (0.15,1.20)	0.42 (0.15,1.18)	0.49 (0.18,1.37)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	2.84 (1.97,4.07)	2.34(1.62,3.75)	1.71 (1.18,2.48)
6.0-<6.5%	11.11 (7.37,16.72)	7.33 (4.81,11.16)	3.86 (2.51,5.94)
≥6.5%	58.23 (36.19,93.70)	37.00 (22.60,60.56)	17.01 (10.26,28.20)
P-value for trend:	<0.001	<0.001	<0.001
Fasting Glucose: 6-year incident diabetes based on elevated fasting glucose levels (≥126 mg/dl) (N=127 cases)*			
<5%	0.27 (0.04,1.99)	0.28 (0.04,2.06)	0.33 (0.04,2.47)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	2.80 (1.29,4.93)	2.26(1.28,3.99)	1.50 (0.85,2.67)
6.0-<6.5%	23.62 (13.61,41.01)	15.45 (8.81,27.09)	7.04 (3.96,12.51)
≥6.5%	66.07 (33.40,130.71)	41.35 (20.52,83.30)	15.03(7.30,30.91)
P-value for trend:	<0.001	<0.001	<0.001
Self-reported Diagnosis: 6-year incident diabetes based on self-reported physician diagnosis (N=519 cases)			
<5%	0.62 (0.28,1.35)	0.63 (0.29,1.38)	0.74 (0.34,1.63)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	3.01 (2.18,4.15)	2.59(1.87,3.58)	1.75 (1.26,2.43)
6.0-<6.5%	11.61 (8.05,16.72)	8.40 (5.76,12.22)	4.01 (2.73,5.88)
≥6.5%	38.66 (23.48,63.64)	25.28 (15.22,42.26)	10.42 (6.19,17.53)
P-value for trend:	<0.001	<0.001	<0.001

* This analysis includes only those individuals with fasting glucose <126 mg/dl at baseline and non-missing glucose measurements during the follow-up visits, N=9,432

Model 1a: Adjusted for age (continuous), sex (male or female), and race (black or white).

Model 2a: Adjusted for variables in Model 1a + LDL- and HDL- cholesterol concentrations (continuous), log-transformed triglycerides (continuous), body-mass index (continuous), waist:hip ratio (continuous), hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, college or above), alcohol intake (current, former, or never), physical activity (continuous), and smoking status (current, former, or never).

Model 3a: Adjusted for all variables in Model 2a + fasting glucose (continuous)

Online Table 2. Adjusted Hazard Ratios of Incident Diabetes, Coronary Heart Disease, Ischemic Stroke, and Death from Any Cause in 10,069 Middle-Aged Adults Without Diagnosed or Undiagnosed Diabetes*, According to Glycated Hemoglobin Category at Baseline

Glycated Hemoglobin Categories	Model 1a	Model 2a	Model 3a
Visit-based diabetes: 6-year incident diabetes based on elevated fasting glucose level (≥126 mg/dl), physician diagnosis, or diabetes medication use (N=614 cases)			
<5.0%	0.51 (0.28,0.92)	0.51 (0.28,0.93)	0.58 (0.32,1.06)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	2.97 (2.37,3.71)	2.49 (1.99,3.12)	1.80 (1.43,2.26)
6.0-<6.5%	13.59 (10.64,17.33)	9.24 (7.20,11.86)	5.11 (3.95,6.61)
≥6.5%	51.24 (37.74)	32.74 (23.89,44.89)	14.46 (10.45,20.00)
P-value for trend:	<.001	<.001	<.001
HbA1c, % (per 1%)	2.72 (2.55,2.90)	2.74 (2.54,2.95)	2.56 (2.34,2.80)
C-statistic	0.7775	0.8264	0.8695
Diagnosed diabetes: 15-year incident diabetes based on self-reported physician diagnosis or diabetes medication use (N=1688 cases)			
<5.0%	0.50 (0.38,0.66)	0.51 (0.39,0.68)	0.56 (0.42,0.73)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	2.07 (1.85,2.32)	1.82 (1.62,2.04)	1.54 (1.37,1.73)
6.0-<6.5%	5.06 (4.36,5.89)	3.65 (3.13,4.27)	2.68 (2.29,3.15)
≥6.5%	12.31 (9.61,15.75)	8.70 (6.76,11.19)	5.63 (4.34,7.28)
P-value for trend:	<.001	<.001	<.001
HbA1c, % (per 1%)	2.19 (2.08,2.31)	2.07 (1.96,2.20)	1.90 (1.77,2.03)
C-statistic	0.6890	0.7438	0.7616
Coronary heart disease (N=1046 cases)			
<5.0%	0.89 (0.68,1.15)	0.97 (0.74,1.25)	0.95 (0.73,1.24)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	1.45 (1.26,1.67)	1.22 (1.06,1.41)	1.25 (1.09,1.45)
6.0-<6.5%	2.42 (1.98,2.96)	1.82 (1.48,2.23)	1.91 (1.54,2.36)
≥6.5%	3.38 (2.25,5.06)	2.30 (1.53,3.46)	2.51 (1.65,3.81)
P-value for trend:	<.001	<.001	<.001
HbA1c, % (per 1%)	1.80 (1.63,1.99)	1.60 (1.42,1.82)	1.64 (1.45,1.86)
C-statistic	0.6968	0.7416	0.7418

Ischemic stroke (N=288 cases)

<5%	0.96 (0.57,1.61)	0.99 (0.59,1.67)	0.97 (0.58,1.63)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	1.21 (0.91,1.60)	1.11 (0.84,1.48)	1.17 (0.88,1.57)
6.0-<6.5%	2.58 (1.82,3.66)	2.19 (1.53,3.13)	2.43 (1.68,3.52)
≥6.5%	3.73 (2.02,6.92)	3.44 (1.84,6.45)	4.09 (2.14,7.83)
P-value for trend:	<.001	<.001	<.001
HbA1c, % (per 1%)	1.75 (1.44,2.11)	1.68 (1.35,2.09)	1.76 (1.42,2.18)
C-statistic	0.7217	0.7606	0.7623

Death from any cause (N=1255 cases)

<5%	1.48 (1.21,1.82)	1.54 (1.26,1.90)	1.54 (1.25,1.89)
5.0-<5.5%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.5-<6.0%	1.33 (1.16,1.51)	1.18 (1.03,1.34)	1.19 (1.04,1.36)
6.0-<6.5%	1.80 (1.50,2.17)	1.49 (1.23,1.81)	1.53 (1.26,1.86)
≥6.5%	2.17 (1.48,3.18)	1.79 (1.22,2.63)	1.86 (1.26,2.76)
P-value for trend:	-	-	-
HbA1c, % (per 1%)	1.35 (1.19,1.52)	1.17 (1.02,1.34)	1.19 (1.03,1.37)
C-statistic	0.6909	0.7344	0.7344

* Participants with a history of diabetes, diabetes medication use, or fasting glucose ≥126 mg/dl at either Visit 1 (1987-1989) or Visit 2 (1990-1992) were excluded.

Model 1a: Adjusted for age (continuous), sex (male or female), and race (black or white).
Model 2a: Adjusted for variables in Model 1a + LDL- and HDL- cholesterol concentrations (continuous), log-transformed triglycerides (continuous), body-mass index (continuous), waist:hip ratio (continuous), hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, college or above), alcohol intake (current, former, or never), physical activity (continuous), and smoking status (current, former, or never).
Model 3a: Adjusted for all variables in Model 2a + fasting glucose (continuous)

Online Table 3. Adjusted* Hazard Ratios for Diagnosed Diabetes, Coronary Heart Disease, Ischemic Stroke, and All-cause Mortality during the 15-Year Study Period, According to Combined Categories of Glycated Hemoglobin and Fasting Glucose at Baseline

Glycated hemoglobin categories	Fasting glucose categories		
	<100 mg/dl	100-<126 mg/dl	≥126 mg/dl
Diagnosed diabetes (N=2251 cases)			
<6.0%	1.00 (ref)	2.12 (1.88,2.40)	6.45 (5.07,8.21)
6.0 to <6.5%	2.88 (2.03,4.09)	5.28 (4.47,6.23)	12.18 (9.87,15.03)
≥6.5%	2.65 (0.66,10.65)†	12.01 (9.36,15.39)	32.05 (26.91,38.18)
Coronary heart disease (N=1198 cases)			
<6.0%	1.00 (ref)	1.04 (0.91,1.19)	0.95 (0.61,1.50)
6.0 to <6.5%	2.48 (1.76,3.48)	1.46 (1.18,1.85)	1.57 (1.09,2.60)
≥6.5%	1.63 (0.23,11.62)†	2.23 (1.52,3.29)	1.62 (1.22,2.15)
Ischemic stroke (N=358 cases)			
<6.0%	1.00 (ref)	0.96 (0.73,1.25)	1.45 (0.70,3.00)
6.0 to <6.5%	2.95 (1.72,5.08)	1.76 (1.20,2.56)	2.13 (1.17,3.87)
≥6.5%	9.33 (2.27,38.45)†	2.47 (1.30,4.70)	2.83 (1.83,4.38)
All-cause mortality (N=1447 cases)			
<6.0%	1.00 (ref)	1.05 (0.93,1.19)	1.03 (0.67,1.57)
6.0 to <6.5%	1.44 (1.03,2.02)	1.40 (1.15,1.71)	1.64 (1.18,2.25)
≥6.5%	2.36 (0.75,7.40)†	1.65 (1.14,2.39)	1.42 (1.08,1.86)

* Adjusted for age (continuous), sex (male or female), race (black or white), LDL- and HDL- cholesterol concentrations (continuous), log-transformed triglycerides (continuous), body-mass index (continuous), waist:hip ratio (continuous), hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, college or above), alcohol intake (current, former, or never), physical activity (continuous), and smoking status (current, former, or never).

†Estimates for the category of individuals with glycated hemoglobin ≥6.5% and fasting glucose <100 mg/dl are highly imprecise and may be unreliable due to the small number of individuals in this group (N=8).

Online Supplemental Material: Model Comparisons

Analyzed models

Model A: all covariates + fasting glucose (continuous)

Model B: all covariates + fasting glucose (continuous) + glycated hemoglobin (continuous)

Model C: all covariates + fasting glucose categories (<100, 100-<126, ≥126 mg/dl)

Model D: all covariates + fasting glucose categories (<100, 100-<126, ≥126 mg/dl) + glycated hemoglobin categories (<6.0, 6.0-6.5, ≥6.5%)

Model E: all covariates + fasting glucose categories (<100, 100-<126, ≥126 mg/dl) + glycated hemoglobin categories (<5.0, 5.0-<5.5, 5.5-<6.0, 6-6.5, ≥6.5%)

Model F: all covariates + glycated hemoglobin (continuous)

Model G: all covariates + glycated hemoglobin categories (<6.0, 6.0-6.5, ≥6.5%)

Comparison of models

Model A vs. Model B (addition of continuous glycated hemoglobin)

Model C vs. Model D (addition of 3 categories of glycated hemoglobin)

Model C vs. Model E (addition of 5 categories of glycated hemoglobin)

Model A vs. Model F (comparison of continuous fasting glucose vs. continuous glycated hemoglobin)

Model C vs. Model G (comparison of 3 fasting glucose categories vs. 3 glycated hemoglobin categories)

Methods of model comparison

We computed 10-year risk for each participant for each outcome for Models A through G from Cox proportional hazard models. We calculated net reclassification improvement (NRI) and integrated discrimination improvement (IDI) and their corresponding p-values according to methods proposed by Pencina et al (Stat Med. 2008; 27:157–172). For NRI, we used four categories of 10-year risk (<5%, 5-<10%, 10-<20%, and ≥20%) for all outcomes.

Results

Diagnosed diabetes

	Model A	Model B	*P*-value	Model C	Model D	Model E	*P*-value[1]	*P*-value[2]
NRI	-	0.049	**<0.001**	-	0.135	0.169	**<0.001**	**<0.001**
IDI	-	0.004	**<0.001**	-	0.031	0.037	**<0.001**	**<0.001**

	Model A	Model F	*P*-value	Model C	Model G	*P*-value
NRI	-	0.063	**<0.001**	-	0.069	**<0.001**
IDI	-	0.003	**0.009**	-	0.008	**0.028**

[1] Comparison of Model C vs Model D

[2] Comparison of Model C vs Model E

Coronary heart disease

	Model A	Model B	*P*-value	Model C	Model D	Model E	*P*-value[1]	*P*-value[2]
NRI	-	0.027	**0.015**	-	0.047	0.053	**<0.001**	**<0.001**
IDI	-	0.003	**<0.001**	-	0.004	0.004	**<0.001**	**<0.001**

	Model A	Model F	*P*-value	Model C	Model G	*P*-value
NRI	-	0.009	**0.194**	-	0.042	**<0.001**
IDI	-	0.001	**0.003**	-	0.003	**<0.001**

[1] Comparison of Model C vs Model D

[2] Comparison of Model C vs Model E

Ischemic stroke

	Model A	Model B	*P*-value	Model C	Model D	Model E	*P*-value[1]	*P*-value[2]
NRI	-	0.025	**0.095**	-	0.067	0.055	**0.001**	**0.010**
IDI	-	0.001	**0.053**	-	0.004	0.004	**<0.001**	**<0.001**

	Model A	Model F	*P*-value	Model C	Model G	*P*-value
NRI	-	0.022	**0.079**	-	0.064	**0.004**
IDI	-	0.001	**0.015**	-	0.004	**<0.001**

[1] Comparison of Model C vs Model D

[2] Comparison of Model C vs Model E

Death from any cause

	Model A	Model B	*P*-value	Model C	Model D	Model E	*P*-value[1]	*P*-value[2]
NRI	-	0.009	**0.154**	-	0.021	0.031	**0.009**	**0.002**
IDI	-	0.001	**0.007**	-	0.002	0.003	**<0.001**	**<0.001**

	Model A	Model F	*P*-value	Model C	Model G	*P*-value
NRI	-	0.013	**0.011**	-	0.017	**0.034**
IDI	-	0.001	**0.005**	-	0.002	**<0.001**

[1] Comparison of Model C vs Model D

[2] Comparison of Model C vs Model E