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Association of Hemoglobin A_{1c} with Cardiovascular Disease and Mortality in Adults: The European Prospective Investigation into Cancer in Norfolk

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Background: **Increasing evidence suggests a continuous relationship between blood glucose concentrations and cardiovascular risk, even below diagnostic threshold levels for diabetes.**

Objective: **To examine the relationship between hemoglobin A_{1c}, cardiovascular disease, and total mortality.**

Design: **Prospective population study.**

Setting: **Norfolk, United Kingdom.**

Participants: **4662 men and 5570 women who were 45 to 79 years of age and were residents of Norfolk.**

Measurements: **Hemoglobin A_{1c} and cardiovascular disease risk factors were assessed from 1995 to 1997, and cardiovascular disease events and mortality were assessed during the follow-up period to 2003.**

Results: **In men and women, the relationship between hemoglobin A_{1c} and cardiovascular disease (806 events) and between hemoglobin A_{1c} and all-cause mortality (521 deaths) was continuous and significant throughout the whole distribution. The relationship was apparent in persons without known diabetes. Persons with hemoglobin A_{1c} concentrations less than 5% had the lowest rates of cardiovascular disease and mortality. An increase in hemoglobin A_{1c} of 1 percentage point was associated with a relative risk for death from any cause of 1.24 (95% CI, 1.14 to 1.34; $P < 0.001$) in men and with a relative risk of 1.28 (CI, 1.06 to 1.32; $P < 0.001$) in women. These relative risks were independent of age, body mass index, waist-to-hip ratio, systolic blood pressure, serum cholesterol concentration, cigarette smoking, and history of cardiovascular disease. When persons with known diabetes, hemoglobin A_{1c} concentrations of 7% or greater, or a history of cardiovascular disease were excluded, the result was similar (adjusted relative risk, 1.26 [CI, 1.04 to 1.52]; $P = 0.02$). Fifteen percent (68 of 521) of the deaths in the sample occurred in persons with diabetes (4% of the sample), but 72% (375 of 521) occurred in persons with HbA_{1c} concentrations between 5% and 6.9%.**

Limitations: **Whether HbA_{1c} concentrations and cardiovascular disease are causally related cannot be concluded from an observational study; intervention studies are needed to determine whether decreasing HbA_{1c} concentrations would reduce cardiovascular disease.**

Conclusions: **The risk for cardiovascular disease and total mortality associated with hemoglobin A_{1c} concentrations increased continuously through the sample distribution. Most of the events in the sample occurred in persons with moderately elevated HbA_{1c} concentrations. These findings support the need for randomized trials of interventions to reduce hemoglobin A_{1c} concentrations in persons without diabetes.**

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See related article on pp 421-431 and editorial comment on pp 475-476.

Diabetes mellitus is of major and increasing global public health importance (1). Persons with diabetes are at increased risk for premature disability and death associated with vascular, renal, retinal, and neuropathic complications. Raised fasting and postchallenge blood glucose levels in an oral glucose tolerance test are used to diagnose diabetes. The diagnostic threshold is based on the shape of the risk curve between glucose levels and specific microvascular complications of diabetes (2–6). Diabetes also increases the risk for macrovascular diseases, such as coronary heart disease and stroke (7). In contrast to microvascular disease, increasing evidence suggests that the relationship between blood glucose level and macrovascular disease is continuous and does not have an obvious threshold (2, 8, 9).

Hemoglobin A_{1c} concentration is an indicator of average blood glucose concentrations over the preceding 3 months; it is useful for characterizing dysglycemia in population studies because it is simpler to perform than the oral glucose tolerance test (10). In a 3-year follow-up of men in a prospective study, we previously reported that hemoglobin A_{1c} concentrations were related to cardiovascular disease and all-cause mortality (11). However, we had insufficient power to examine risk relationships at concentrations close to the diagnostic threshold of 7% or to examine the relationship in women.

We report the relation between hemoglobin A_{1c} concentrations and fatal and nonfatal coronary heart disease, cardiovascular disease events, and all-cause mortality in men and women after an average of 6 years of follow-up.

Methods

The European Prospective Investigation into Cancer in Norfolk (EPIC–Norfolk) is a prospective population study of 25 623 men and women who were between 40 and 79 years of age and who resided in Norfolk, United Kingdom. Participants were recruited from general practice registers. Information on the recruitment process is available elsewhere (12). Between 1993 and 1997, participants completed a health and lifestyle questionnaire. Participants

Context

Several studies suggest that blood glucose levels are associated with cardiovascular disease, even at blood glucose values that do not meet diagnostic criteria for diabetes.

Contribution

Among adult residents of Norfolk, United Kingdom, there was a continuous relationship between hemoglobin A_{1c} levels and cardiovascular disease and total mortality. This relationship was apparent even among persons without diabetes.

Implications

These observations justify the need for studies that address whether improvements in glycemic control might improve health outcomes in persons who do not have diabetes.

–The Editors

were asked whether a doctor had ever told them that they have any of the conditions contained in a list that included diabetes, heart attack, and stroke. People with known diabetes were defined as those who responded "yes" to the diabetes option of this question. Smoking history was derived from responses (yes or no) to the questions: "Have you ever smoked as much as 1 cigarette a day for as long as a year?" and "Do you smoke cigarettes now?"

At a clinic, trained nurses performed a health examination for each participant. Body mass index was estimated as weight (kg)/height (m^2), and waist-to-hip ratio was determined by measurements of the circumference of the waist and hips. Blood pressure was measured by using an Accutorr (Datascope, Mahwah, New Jersey) noninvasive blood pressure monitor after the participant had been seated for 5 minutes. The mean of 2 readings was used for analysis. Nonfasting blood samples were taken; samples for assay were stored in a refrigerator at 4 °C until transport within 1 week of sampling to the Department of Clinical Biochemistry, University of Cambridge. Starting in 1995, hemoglobin A_{1c} was measured on fresh EDTA blood samples by using high-performance liquid chromatography (BioRad Diamat Automated Glycosylated Haemoglobin Analyser, Hemel Hempstead, United Kingdom).

We report results for follow-up to January 2003, an average of about 6 years. All participants were flagged for death certification at the Office of National Statistics; vital status was obtained for the entire cohort. Trained nosologists coded death certificates according to the International Classification of Diseases, Ninth or Tenth Revisions (ICD-9 or ICD-10). Cardiovascular death (stroke, coronary heart disease, and other vascular causes) was defined as those whose underlying cause of death was coded as ICD-9 400–448 or ICD-10 I10–I79. Death from coronary heart disease was defined as those whose cause of death was coded as ICD-9 410–414 or ICD-10 I22–I25.

Participants admitted to a hospital were identified by their National Health Service number. Hospitals were

Table 1. **Distribution of Variables by Hemoglobin A_{1c} Concentration and Known Diabetes in 4662 Men and 5570 Women Age 45 to 79 Years (European Prospective Investigation into Cancer in Norfolk, 1995 to 1997)***

	Hemoglobin A_{1c} Concentration		
	<5%	**5%–5.4%**	**5.5%–5.9%**
Men, *n*	1204	1606	1153
Age, *y*	7.5 ± 8.6	58.8 ± 9.0	60.5 ± 8.5
Body mass index, *kg/m²*	26.2 ± 3.0	26.5 ± 3.2	26.6 ± 3.4
Waist-to-hip ratio, *cm/cm*	0.93 ± 0.06	0.93 ± 0.06	0.93 ± 0.06
Systolic blood pressure, *mm Hg*	136.3 ± 16.7	136.9 ± 16.8	137.4 ± 17.7
Cholesterol level, *mmol/L (mg/dL)*	5.88 ± 1.07 (227 ± 41)	6.01 ± 1.04 (233 ± 40)	6.09 ± 1.06 (236 ± 41)
LDL cholesterol level, *mmol/L (mg/dL)*	3.81 ± 0.94 (147 ± 36)	3.89 ± 0.95 (151 ± 36)	3.95 ± 0.92 (153 ± 36)
HDL cholesterol level, *mmol/L (mg/dL)*	1.26 ± 0.34 (49 ± 13)	1.26 ± 0.36 (49 ± 14)	1.25 ± 0.33 (48 ± 13)
Triglyceride level, *mmol/L (mg/dL)*	1.91 ± 1.08 (170 ± 96)	2.00 ± 1.12 (177 ± 99)	2.06 ± 1.13 (182 ± 100)
Current cigarette smoking, *n (%)*	100 (8.4)	168 (10.6)	183 (16.0)
History of heart attack or stroke, *n (%)*	50 (4.2)	89 (5.5)	85 (7.4)
Women, *n*	1562	1967	1378
Age, *y*	55.4 ± 8.1	58.1 ± 8.6	61.2 ± 8.6
Body mass index, *kg/m²*	25.4 ± 3.8	26.1 ± 4.3	26.5 ± 4.5
Waist-to-hip ratio, *cm/cm*	0.78 ± 0.06	0.79 ± 0.06	0.80 ± 0.06
Systolic blood pressure, *mm Hg*	130.2 ± 17.8	133.1 ± 18.2	137.0 ± 19.2
Cholesterol level, *mmol/L (mg/dL)*	6.01 ± 1.10 (232 ± 42)	6.28 ± 1.13 (242 ± 44)	6.50 ± 1.21 (251 ± 47)
LDL cholesterol level, *mmol/L (mg/dL)*	3.78 ± 1.03 (146 ± 40)	3.98 ± 1.04 (154 ± 40)	4.14 ± 1.10 (160 ± 43)
HDL cholesterol level, *mmol/L (mg/dL)*	1.63 ± 0.54 (63 ± 21)	1.61 ± 0.42 (62 ± 16)	1.59 ± 0.42 (61 ± 16)
Triglyceride level, *mmol/L (mg/dL)*	1.51 ± 0.73 (125 ± 64)	1.57 ± 0.84 (139 ± 74)	1.73 ± 0.94 (153 ± 82)
Current cigarette smoking, *n (%)*	137 (8.8)	229 (11.8)	167 (12.2)
History of heart attack or stroke, *n (%)*	27 (1.7)	35 (1.8)	35 (2.5)

* Values expressed with a plus/minus sign are the mean ± SD. $P < 0.001$ for differences between categories for all variables. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

linked to the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for Norfolk residents. We used the same ICD diagnostic codes described in the preceding paragraphs to ascertain hospital episodes of cardiovascular disease and coronary heart disease in our cohort.

Participants were identified as having a coronary heart disease event during follow-up if they had a hospital admission or died with coronary heart disease as the cause of death. Of the coronary heart disease events identified, 21% (112 of 529) were fatal; of the cardiovascular disease events, 23% (197 of 806) were fatal. In men, 24% (76 of 321) of deaths were attributed to heart disease and 29% (117 of 321) were attributed to cardiovascular disease. In women, 18% (36 of 200) of deaths were attributed to heart disease and 35% (70 of 200) were attributed to cardiovascular causes.

The Norwich Ethics Committee approved the study, and participants gave signed informed consent.

Statistical Analysis

These analyses, undertaken by using SPSS software, version 10.0 (SPSS, Inc., Chicago, Illinois), included 10 232 men and women age 45 to 79 years who completed the health and lifestyle questionnaire and had available hemoglobin A_{1c} measurements. We divided the cohort into 7 categories on the basis of baseline data: known diabetes, high likelihood of previously undiagnosed diabetes (no personal history of diabetes but a hemoglobin A_{1c} concentration ≥7%), and hemoglobin A_{1c} concentrations in 0.5–percentage point intervals (<5%, 5% to 5.4%, 5.5% to 5.9%, 6.0% to 6.4%, and 6.5% to 6.9%). We examined risk factor distributions and then coronary heart disease, cardiovascular disease, and all-cause mortality rates by hemoglobin A_{1c} and diabetes category. Age-adjusted odds ratios were calculated by using logistic regression models. We used a Cox proportional hazards model to determine the independent contribution of hemoglobin A_{1c} to total mortality and cardiovascular and coronary heart disease after adjustment for age, body mass index, waist-to-hip ratio, systolic blood pressure, blood cholesterol concentrations, cigarette smoking, and history of heart attack or stroke. Participants with missing baseline data for 1 or more risk factors (130 men and 186 women) were excluded from the multivariate analyses.

Role of the Funding Sources

The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Table 1 presents characteristics of the participants according to hemoglobin A_{1c} concentration and self-reported diabetes. Those with known diabetes had higher mean (±SD) hemoglobin A_{1c} concentrations (8.0% ± 1.9%) than the rest of the study sample (5.3% ± 0.7%). They were older and had a higher body mass index, waist-to-hip ratio, and systolic blood pressure; they were also more

Table 1—**Continued**

Hemoglobin A_{1c} Concentration			Known Diabetes
6%–6.4%	6.5%–6.9%	≥7%	
374	84	81	160
62.4 ± 8.3	64.3 ± 7.4	64.0 ± 7.9	64.4 ± 7.4
27.3 ± 3.8	28.3 ± 3.8	28.6 ± 3.4	27.7 ± 3.8
0.95 ± 0.06	0.96 ± 0.05	0.97 ± 0.05	0.96 ± 0.09
140.5 ± 17.2	142.3 ± 84	143.8 ± 16.0	143.4 ± 19.3
6.19 ± 1.25 (239 ± 48)	6.12 ± 1.04 (237 ± 40)	6.22 ± 1.04 (241 ± 40)	5.90 ± 1.21 (228 ± 47)
3.94 ± 0.99 (152 ± 38)	3.96 ± 0.97 (153 ± 37)	3.90 ± 0.93 (151 ± 36)	3.65 ± 10.2 (141 ± 40)
1.21 ± 0.31 (47 ± 12)	1.19 ± 0.32 (46 ± 12)	1.10 ± 0.28 (43 ± 11)	1.15 ± 0.28 (45 ± 11)
2.34 ± 1.52 (207 ± 135)	2.34 ± 1.61 (207 ± 142)	2.80 ± 1.78 (247 ± 126)	2.60 ± 1.78 (230 ± 158)
72 (19.4)	19 (22.6)	10 (12.3)	12 (7.5)
43 (11.5)	14 (16.7)	15 (18.5)	32 (20.0)
439	73	68	83
63.4 ± 7.9	63.8 ± 7.6	65.8 ± 6.7	63.1 ± 7.6
27.5 ± 4.7	28.1 ± 5.9	30.7 ± 5.7	28.1 ± 5.3
0.82 ± 0.06	0.83 ± 0.07	0.86 ± 0.08	0.83 ± 0.07
139.2 ± 18.0	142.1 ± 17.5	145.3 ± 21.1	142.6 ± 20.8
6.79 ± 1.23 (262 ± 47)	6.87 ± 1.28 (266 ± 49)	6.56 ± 1.26 (254 ± 49)	6.43 ± 1.07 (248 ± 41)
4.31 ± 1.12 (166 ± 43)	4.37 ± 1.05 (169 ± 41)	4.12 ± 0.92 (159 ± 36)	4.08 ± 0.92 (158 ± 36)
1.54 ± 0.44 (60 ± 17)	1.44 ± 0.39 (56 ± 15)	1.37 ± 0.48 (53 ± 19)	1.52 ± 0.39 (59 ± 15)
2.12 ± 1.29 (188 ± 114)	2.20 ± 1.10 (195 ± 98)	2.36 ± 1.10 (209 ± 98)	2.05 ± 1.13 (181 ± 100)
6.4 (14.8)	14 (19.2)	11 (16.4)	3 (3.6)
17 (3.9)	1 (1.4)	3 (4.4)	9 (10.8)

Table 2. **Rates and Age-Adjusted Relative Risks for Total Coronary Heart Disease Events, Cardiovascular Disease Events, and All-cause Mortality by Category of Hemoglobin A_{1c} Concentration and Known Diabetes in 4462 Men and 5570 Women Age 45 to 79 Years (European Prospective Investigation into Cancer in Norfolk, 1995 to 2003)***

Variable	Hemoglobin A_{1c} Concentration						Known Diabetes
	<5%	5%–5.4%	5.5%–5.9%	6%–6.4%	6.5%–6.9%	≥7%	
Men, *n*	1204	1606	1153	374	84	81	160
Coronary heart disease events							
Events/100 persons	3.8	6.4	8.7	10.2	16.7	28.4	21.9
Events, *n*	46	102	100	38	14	23	35
Age-adjusted relative risk (95% CI)	1.00	1.56 (1.09–2.24)	2.00 (1.39–2.88)	2.13 (1.35–3.35)	3.44 (1.78–6.63)	7.07 (3.96–12.62)	4.82 (2.96–7.85)
Cardiovascular disease events							
Events/100 persons	6.7	9.0	12.1	15.2	25.0	34.8	26.9
Events, *n*	81	144	140	57	21	28	43
Age-adjusted relative risk (95% CI)	1.00	1.23 (0.92–1.64)	1.56 (1.16–2.09)	1.79 (1.24–2.60)	3.03 (1.73–5.31)	5.01 (2.95–8.51)	3.32 (2.16–5.10)
All-cause mortality							
Events/100 persons	3.8	5.5	7.5	9.9	19.0	18.5	20.0
Events, *n*	46	88	87	37	16	15	32
Age-adjusted relative risk (95% CI)	1.00	1.25 (0.88–1.82)	1.57 (1.08–2.29)	1.80 (1.13–2.86)	3.49 (1.83–6.66)	3.38 (1.74–6.53)	3.68 (2.22–6.09)
Women, *n*	1562	1967	1378	439	73	68	83
Coronary heart disease events							
Events/100 persons	1.7	2.1	3.0	7.3	9.6	16.2	15.7
Events, *n*	26	41	41	32	7	11	13
Age-adjusted relative risk (95% CI)	1.00	0.96 (0.58–1.59)	1.04 (0.62–1.63)	2.29 (1.34–3.96)	3.06 (1.25–7.49)	4.73 (2.16–10.34)	6.00 (2.90–12.44)
Cardiovascular disease events							
Events/100 persons	3.3	3.8	5.4	9.8	13.7	36.8	18.1
Events, *n*	51	74	74	43	10	25	15
Age-adjusted relative risk (95% CI)	1.00	0.89 (0.62–1.29)	0.98 (0.68–1.44)	1.63 (1.05–2.52)	2.37 (1.13–5.01)	7.96 (4.38–14.5)	3.63 (1.90–6.93)
All-cause mortality							
Events/100 persons	2.0	2.7	4.4	6.4	6.8	25.0	4.9
Events, *n*	32	53	61	28	5	17	4
Age-adjusted relative risk (95% CI)	1.00	1.02 (0.65–1.60)	1.28 (0.82–2.01)	1.61 (0.94–2.75)	1.70 (0.63–4.60)	6.91 (3.50–13.67)	1.26 (0.43–3.72)

* $P < 0.001$ for linear trend across hemoglobin A_{1c} categories for all end points. Age-adjusted relative risks were determined by using logistic regression models.

likely to report having had a previous heart attack or stroke. Participants with probable but previously undiagnosed diabetes (hemoglobin $A_{1c} \geq 7\%$) shared these characteristics. Mean risk factor levels rose with increasing concentration of hemoglobin A_{1c} less than 7%.

Table 2 shows adjusted odds ratios for hemoglobin A_{1c} concentrations, diabetes status, and outcomes. Persons with known or undiagnosed diabetes had a greater risk for all-cause mortality and cardiovascular or coronary heart disease than those without diabetes. Risk for coronary heart or cardiovascular disease and total mortality increased throughout the whole range of hemoglobin A_{1c} concentrations; those with hemoglobin A_{1c} concentrations less than 5% had the lowest rates. For men, a gradient of increasing rates through the distribution was apparent for all end points. For women, odds ratios for cardiovascular or coronary heart disease did not increase significantly until the hemoglobin A_{1c} concentration reached 6%; odds ratios were very high in women with concentrations greater than 7%.

Table 3 shows outcomes after adjustment for age alone and then after adjustment for age and other risk factors. In men, known diabetes predicted coronary heart and cardiovascular disease events and total mortality with approximate 2-fold relative risks. These relative risks were only slightly attenuated after adjustment for known risk factors. In women, known diabetes status predicted an approximate 5-fold increase in risk for coronary heart and 3-fold increase in risk for cardiovascular disease events; these increases were attenuated after adjustment for known risk factors to 3-fold and 2-fold risk, respectively. In men and women, hemoglobin A_{1c} concentrations predicted an increased risk for coronary heart and cardiovascular disease events and total mortality. This was independent of and only slightly attenuated after adjustment for known risk factors. When high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were substituted for cholesterol in the model, results were similar (data not shown). When known diabetes status and hemoglobin A_{1c} concentration were included in the same model, diabetes was no longer a significant independent predictor of cardiovascular disease or death. The significantly increased risk for diabetes with mortality seemed to be entirely mediated through hemoglobin A_{1c} concentration. An increase in hemoglobin A_{1c} concentration of 1 percentage

point was associated with a 20% to 30% increase in event rates.

We conducted multivariate regressions after excluding all persons who reported a history of heart disease or stroke at baseline and who had a history of diabetes or hemoglobin A_{1c} concentration of 7% or greater. The relative risk associated with a 1–percentage point increase in hemoglobin A_{1c} concentration, after adjustment for age, sex, and risk factor, was 1.40 (CI, 1.14 to 1.73; $P = 0.002$) for coronary heart disease (301 of 9165), 1.16 (CI, 0.99 to 1.36; $P = 0.08$) for cardiovascular disease (523 of 9165), and 1.26 (CI, 1.04 to 1.52; $P = 0.02$) for total mortality (369 of 9165).

Discussion

Established diabetes was a strong risk factor for coronary heart disease, cardiovascular disease, and total mortality. The increased risks for diabetes seemed to be mediated almost entirely through hemoglobin A_{1c} concentration because diabetes was no longer significant when hemoglobin A_{1c} was included in the regression model. Hemoglobin A_{1c} significantly predicted all-cause mortality and coronary and cardiovascular disease, even below the threshold commonly accepted for the diagnosis of diabetes and independent of age and classic risk factors. The gradient was apparent through the population range from less than 5% to 6.9%. An increase in hemoglobin A_{1c} of 1 percentage point was associated with a 20% to 30% increase in mortality or cardiovascular events.

Although the number of persons in the category of hemoglobin A_{1c} concentrations greater than 7% and category of known diabetes is small, in these analyses, persons with known diabetes had lower event rates than those with newly diagnosed diabetes who had hemoglobin A_{1c} concentrations greater than 7%. There is some evidence (**Table 1**) that people with known diabetes were better treated for established cardiovascular risk factors, such as hyperlipidemia, hypertension, and smoking.

Table 3. **Separate Cox Multivariate Regression Models for Coronary Heart Disease Events, Cardiovascular Disease Events, and All-Cause Mortality in 4662 Men and 5570 Women Age 45 to 79 Years (European Prospective Investigation into Cancer in Norfolk, 1995 to 2003)***

Variable	Model	Age-Adjusted Relative Risk (95% CI)	*P* Value	Age- and Risk Factor–Adjusted Relative Risk (95% CI)†	*P* Value
Men					
Coronary heart disease, *n*/*n*‡		358/4662		342/4532	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.36 (1.28–1.46)	<0.001	1.25 (1.16–1.34)	<0.001
Model 2	Diabetes history (yes vs. no)	2.42 (1.68–3.47)	<0.001	1.87 (1.30–2.71)	<0.001
Model 3	HbA_{1c} (per 1–percentage point increase)	1.37 (1.25–1.48)	<0.001	1.25 (1.14–1.38)	<0.001
	Diabetes history (yes vs. no)	1.00 (0.64–1.57)	>0.2	0.99 (0.62–1.59)	>0.2
Cardiovascular disease, *n*/*n*‡		514/4662		498/4532	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.30 (1.22–1.38)	<0.001	1.21 (1.13–1.29)	<0.001
Model 2	Diabetes history (yes vs. no)	2.18 (1.59–2.99)	<0.001	1.81 (1.31–2.49)	<0.001
Model 3	HbA_{1c} (per 1–percentage point increase)	1.28 (1.19–1.38)	<0.001	1.19 (1.10–1.29)	<0.001
	Diabetes history (yes vs. no)	1.10 (0.75–1.63)	>0.2	1.16 (0.78–1.72)	>0.2
All-cause mortality, *n*/*n*‡		321/4662		306/4532	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.29 (1.20–1.40)	<0.001	1.24 (1.14–1.34)	<0.001
Model 2	Diabetes history (yes vs. no)	2.29 (1.58–3.32)	<0.001	1.94 (1.31–2.87)	<0.001
Model 3	HbA_{1c} (per 1–percentage point increase)	1.26 (1.14–1.39)	<0.001	1.22 (1.10–1.35)	<0.001
	Diabetes history (yes vs. no)	1.24 (0.77–1.98)	>0.2	1.14 (0.69–1.87)	>0.2
Women					
Coronary heart disease, *n*/*n*‡		171/5570		157/5384	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.37 (1.26–1.49)	<0.001	1.20 (1.07–1.34)	<0.001
Model 2	Diabetes history (yes vs. no)	4.69 (2.67–8.26)	<0.001	2.71 (1.48–4.98)	<0.001
Model 3	HbA_{1c} (per 1–percentage point increase)	1.31 (1.19–1.45)	<0.001	1.13 (0.98–1.30)	0.08
	Diabetes history (yes vs. no)	2.11 (1.09–4.06)	0.03	1.91 (0.91–4.01)	0.09
Cardiovascular disease, *n*/*n*‡		292/5570		273/5384	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.33 (1.24–1.42)	<0.001	1.21 (1.11–1.31)	<0.001
Model 2	Diabetes history (yes vs. no)	2.96 (1.77–4.97)	<0.001	1.89 (1.09–3.23)	0.02
Model 3	HbA_{1c} (per 1–percentage point increase)	1.31 (1.21–1.41)	<0.001	1.21 (1.10–1.34)	<0.001
	Diabetes history (yes vs. no)	1.35 (0.76–2.41)	>0.2	1.03 (0.54–1.97)	>0.2
All-cause mortality, *n*/*n*‡		200/5570		189/5384	
Model 1	HbA_{1c} (per 1–percentage point increase)	1.28 (1.17–1.41)	<0.001	1.28 (1.06–1.32)	<0.01
Model 2	Diabetes history (yes vs. no)	1.03 (0.38–2.76)	>0.2	0.71 (0.26–1.93)	>0.2
Model 3	HbA_{1c} (per 1–percentage point increase)	1.32 (1.20–1.45)	<0.001	1.25 (1.12–1.41)	<0.001
	Diabetes history (yes vs. no)	0.45 (1.59–1.26)	0.13	0.36 (0.12–1.05)	0.06

* See Appendix Table (available at www.annals.org) for data on other covariates. HbA_{1c} = hemoglobin A_{1c}.
† Risk factors are systolic blood pressure, serum cholesterol level, body mass index, waist-to-hip ratio, cigarette smoking, and history of myocardial infarction or stroke.
‡ Denotes number of events/total in analyses; multivariate analyses have lower numbers because of missing data.

We previously reported findings for mortality after 3 years of follow-up in men only (11). At that time, we did not have data on nonfatal cardiovascular disease events or sufficient power to examine the relationship in women. With this 6-year follow-up, the relative risk estimates for total fatal and nonfatal cardiovascular disease were similar to those that we observed previously for cardiovascular mortality; they were also consistent for men and women. In addition, we examined the stepwise gradient of risk for finer groupings of hemoglobin A_{1c} concentrations (between 5.5% and 6.9%); such analyses were not previously possible.

Although associations between hemoglobin A_{1c} and recognized cardiovascular risk factors were strong, the increased mortality and cardiovascular risks were independent of blood pressure, serum cholesterol or lipid profiles, body mass index, waist-to-hip ratio, cigarette smoking, and history of heart disease or stroke. In addition, these associations were consistent after we excluded persons with existing diabetes, heart disease, and stroke. Nevertheless, we cannot rule out residual confounding with other known and unknown risk factors, such as inflammatory markers or family predisposition (not available in these analyses), but the magnitude of association of hemoglobin A_{1c} concentration with mortality and cardiovascular events is larger than has been reported for these other risk factors.

Substantial measurement errors in determining hemoglobin A_{1c} concentrations and cardiovascular disease outcomes probably occurred in our analyses. We did not have information on specific medications that may affect glucose metabolism, and we had only 1 measure of hemoglobin A_{1c} at 1 time point for each participant.

Four fifths of the cardiovascular events were nonfatal; they were identified by linking records with hospital admission data. Although we could ascertain all deaths in the cohort, we could not confidently identify all nonfatal cardiovascular events. Hospital admission data probably underestimate nonfatal cardiovascular events because many of these events do not result in hospital admission. Nevertheless, this method probably identifies nonfatal events of most clinical importance, that is, those resulting in hospital admission. While self-reported nonfatal events, a method used in many studies, may identify nonhospitalized persons, these studies rely on responses to follow-up questionnaires. These questionnaires are usually incomplete in prospective studies and may therefore result in incomplete, and possibly biased, ascertainment. Diagnostic codes for cardiovascular disease on death certificates may be inaccurate (13). Underestimation or random misclassification of cardiovascular events in our cohort may have attenuated the relationship with hemoglobin A_{1c}.

Persons with known diabetes may be more likely to be admitted to a hospital with a diagnosis of cardiovascular disease. However, this type of bias would not explain the trends for total mortality and the dose–response relationship with hemoglobin A_{1c} in people without known diabetes.

Debate continues about which measure of glucose metabolism should be used to characterize populations and determine diagnostic categories. Comparisons of the predictive ability of fasting and 2-hour blood glucose levels and hemoglobin A_{1c} concentration suggest that they are equal predictors of the microvascular complications of diabetes. Prospective studies generally report a flat relationship below a threshold for fasting, postchallenge blood glucose levels, and hemoglobin A_{1c} concentration for microvascular complications (3–5).

Some early studies reported variable results for the relationship between blood glucose levels and macrovascular disease (14–20); however, power was limited. Several meta-analyses have suggested that the relationship between blood glucose concentrations and cardiovascular events is more linear and does not have an obvious threshold (8, 9). Few prospective studies with all 3 measures of glucose metabolism are large enough to compare their relative abilities to predict macrovascular disease. In the Rancho Bernardo Study (17) of nondiabetic men and women, hemoglobin A_{1c} concentration, but not fasting blood glucose or postchallenge blood glucose level, was significantly related to cardiovascular disease and ischemic heart disease mortality in women but not men, independent of other risk factors measured (17). The Hoorn population study (18) reported that postchallenge blood glucose and hemoglobin A_{1c} values in persons without diabetes were associated with an increased risk for cardiovascular disease. However, these increased risks were largely, but not completely, attributable to known cardiovascular risk factors. The Framingham Offspring study (20) reported that fasting blood glucose, 2-hour postchallenge blood glucose, and hemoglobin A_{1c} tests were individually significant predictors of cardiovascular disease; however, when modeled together, 2-hour postchallenge blood glucose was the measure that remained independently predictive of cardiovascular disease. Different measures of glucose metabolism may contribute independent information and, in direct comparisons, may have different predictive values; nevertheless, hemoglobin A_{1c}, a more feasible measure for large population studies, seems to be comparable to the other measures of glucose metabolism in terms of individual predictive value for cardiovascular disease and total mortality.

Data in women are scarce. In the 20 prospective studies included in meta-analyses of the relationship between blood glucose levels and coronary heart disease (8, 9), 94% of the individuals studied were men. In the Rancho Bernardo Study (19), coronary heart disease mortality rates increased linearly with fasting blood glucose in nondiabetic men, but a threshold relationship at 6.1 mmol/L (110 mg/dL) was noted in women. Results for women in EPIC–Norfolk suggest a less linear relationship between hemoglobin A_{1c} and cardiovascular disease in women than in men; risk for coronary heart disease among men is already sig-

nificantly increased in those with hemoglobin A_{1c} concentrations of 5.0% to 5.4% compared with those with hemoglobin A_{1c} concentrations less than 5%. In women, coronary risk was significantly increased only at a hemoglobin A_{1c} concentration of 6% or greater. However, this could be due to lack of power with lower event rates in women. In regression analyses, although the absolute rates were lower in women than in men, the relative risks associated with a given increase in hemoglobin A_{1c} concentration were similar in women and men.

Our findings confirm that men and women with diabetes have an increased risk for cardiovascular disease and total mortality. Much attention has focused on microvascular events, the specific complications of diabetes. However, in the United Kingdom Prospective Diabetes Study (UKPDS), myocardial infarction and stroke (22.4 cases/1000 patient-years) outnumbered microvascular event rates (11.4 cases/1000 patient-years). Strict control of blood glucose significantly reduced microvascular complications by 25%, but the study had inadequate power to detect a smaller difference (10%) in diabetes-related mortality (21). Nevertheless, the UKPDS reported that control of other cardiovascular risk factors, such as hypertension, in persons with diabetes was of particular benefit in preventing adverse macrovascular outcomes (32% reduction in diabetes-related deaths) (22). Trials have demonstrated the effectiveness of combined cardiovascular risk reduction, including blood pressure and cholesterol lowering, as well as control of blood glucose levels in reducing cardiovascular events in persons with clinically diagnosed diabetes (23).

For blood cholesterol, the debate about whom to treat has shifted from basing treatment decisions on blood levels toward assessing absolute cardiovascular risk (24–26). This focuses attention on those at highest risk, who have most to gain from risk reduction. It may be timely to consider the inclusion of hemoglobin A_{1c} concentrations in cardiovascular risk tables so that therapeutic decisions can be based on better characterization of absolute risk.

Persons with hemoglobin A_{1c} concentrations less than 5%, who made up one quarter of the sample, had the lowest rates for mortality and cardiovascular disease. Those with known or newly diagnosed diabetes (hemoglobin A_{1c} concentration $\geq$ 7%) made up 4% of this sample but contributed about 25% of the excess mortality associated with hemoglobin A_{1c} concentrations greater than 5%. Targeting this group for preventive interventions is crucial. However, 75% of the population excess mortality associated with hemoglobin A_{1c} concentrations greater than 5% occurred in the large percentage of persons who had hemoglobin A_{1c} concentrations between 5% and 6.9%.

Prevention trials in persons with impaired glucose tolerance demonstrate that lifestyle and pharmacologic intervention can reduce progression to diabetes (27, 28). Such interventions would also probably diminish the risk for macrovascular complications, but this is not yet proven. A recent trial indicates that control of blood glucose levels, together with other cardiovascular risk factors, can reduce cardiovascular events (23). Some authorities (29) have proposed screening the population for impaired glucose tolerance or the broader category of prediabetes. Although this individualized approach to prevention may be successful, the potential harms of labeling people with these conditions as diseased are unknown. Both population efforts and individualized approaches will probably be required (30). Our data suggest that if there were a causal relationship between hemoglobin A_{1c} and mortality and the effect we observed was entirely due to hemoglobin A_{1c} concentration, a reduction in hemoglobin A_{1c} concentration of 0.1 percentage point in everyone in the population without diabetes has the potential to reduce total mortality by up to 6%. A causal relationship still needs to be more definitively established, but hemoglobin A_{1c} changes of this magnitude are feasible. In the Diabetes Prevention Program (28), the mean difference in hemoglobin A_{1c} between the placebo and lifestyle intervention group was 0.2 percentage point, but this required intensive individualized support for a group at very high risk. The challenge would be to find practical ways of shifting the population mean by interventions aimed at the large group of individuals at modest risk; this strategy is likely to have the biggest impact on the burden of macrovascular disease associated with dysglycemia. We have previously reported relationships between dietary patterns, such as fat intake or low fruit and vegetable intake, and hemoglobin A_{1c} concentrations (31, 32). Although such observed associations need to be further tested, trials demonstrating the value of behavioral interventions, such as physical activity and weight control, in the primary prevention of diabetes indicate that surprisingly modest changes substantially reduce risk (27, 28). We would expect such behavioral changes to influence glucose metabolism, even at lower concentrations. The increasing prevalence of diabetes in the population indicates that glucose tolerance is highly susceptible to environmental factors.

Our study highlights the independent relationship of blood glucose concentrations to cardiovascular and mortality risk in men and women in the general population and supports the need for randomized, controlled trials of interventions to assess the effect of reduced hemoglobin A_{1c} concentrations on cardiovascular events in persons without diabetes.

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Appendix Table. **Cox Multivariate Regression Model for Coronary Heart Disease, Cardiovascular Disease, and All-Cause Mortality in 10232 Men and Women Age 45 to 79 Years (European Prospective Investigation into Cancer in Norfolk, 1995–2003): Complete Data for all Covariates***

Variable	Relative Risk (95% CI)		
	Coronary Heart Disease (n = 499 events)	Cardiovascular Disease (n = 771 events)	All-Cause Mortality (n = 495 events)
HbA_{1c} per 1–percentage point increase	1.22 (1.13–1.31)	1.20 (1.12–1.27)	1.22 (1.13–1.32)
Known diabetes (yes vs. no)	1.18 (0.80–1.76)	1.12 (0.80–1.56)	0.92 (0.59–1.41)
Age per 10 y	1.81 (1.60–2.04)	1.97 (1.79–2.17)	2.70 (2.37–3.06)
Body mass index per 3 kg/m^2	1.10 (1.02–1.18)	1.10 (1.04–1.17)	1.00 (0.93–1.08)
Waist-to-hip ratio per 0.06	1.15 (1.06–1.25)	1.14 (1.06–1.22)	1.16 (1.06–1.26)
Systolic blood pressure per 20 mm Hg	1.06 (0.96–1.17)	1.09 (1.01–1.18)	1.03 (0.93–1.14)
Cholesterol per 1 mmol/L	1.16 (1.07–1.25)	1.09 (1.03–1.16)	0.99 (0.91–1.07)
Smoker (current vs. never)	1.91 (1.44–2.56)	1.79 (1.42–2.26)	2.23 (1.68–2.96)
History of cardiovascular disease (yes vs. no)	5.88 (4.79–7.21)	4.15 (3.49–4.96)	2.23 (1.75–2.85)
Sex (women vs. men)	0.66 (0.50–0.87)	0.71 (0.57–0.89)	0.88 (0.68–1.15)

* All covariates were entered into the same model. HbA_{1c} = hemoglobin A_{1c}.

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