Hyperglycemia and Stroke Mortality

Comparison between fasting and 2-h glucose criteria

MARJUKKA HYVÄRINEN, MSC[1]
QING QIAO, MD, PHD[1,2]
JAAKKO TUOMILEHTO, MD, PHD[1,2]
TIINA LAATIKAINEN, MD, PHD[2]
ROBERT J. HEINE, MD, PHD[3]
COEN D.A. STEHOUWER, MD, PHD[4]
K. GEORGE M.M. ALBERTI, MD, PHD[5]
KALEVI PYÖRÄLÄ, MD, PHD[6]
BJÖRN ZETHELIUS, MD, PHD[7]
BIRGITTA STEGMAYR, MD, PHD[8]
FOR THE DECODE STUDY GROUP*

OBJECTIVE — We investigated stroke mortality in individuals in different categories of glycemia and compared hazard ratios (HRs) corresponding to a 1-SD increase in 2-h plasma glucose and fasting plasma glucose (FPG) criteria.

RESEARCH DESIGN AND METHODS — We examined data from 2-h 75-g oral glucose tolerance tests taken from 13 European cohorts comprising 11,844 (55%) men and 9,862 (45%) women who were followed up for a median of 10.5 years. A multivariate adjusted Cox proportional hazards model was used to estimate HRs for stroke mortality.

RESULTS — In men and women without a prior history of diabetes, multivariate adjusted HRs for stroke mortality corresponding to a 1-SD increase in FPG were 1.02 (95% CI 0.83–1.25) and 1.52 (1.22–1.88) and those in 2-h plasma glucose 1.21 (1.06–1.38) and 1.31 (1.06–1.61), respectively. Addition of 2-h plasma glucose to the model with FPG significantly improved prediction of stroke mortality in men ($\chi^2 = 10.12$; $P = 0.001$) but not in women ($\chi^2 = 0.01$; $P = 0.94$), whereas addition of FPG to 2-h plasma glucose improved stroke mortality in women ($\chi^2 = 4.08$; $P = 0.04$) but not in men ($\chi^2 = 3.29$; $P = 0.07$).

CONCLUSIONS — Diabetes defined by either FPG or 2-h plasma glucose increases the risk of stroke mortality. In individuals without a history of diabetes, elevated 2-h postchallenge glucose is a better predictor than elevated fasting glucose in men, whereas the latter is better than the former in women.

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Several epidemiological studies have indicated that diabetes is a major risk factor for stroke (1) and stroke recurrence (2). Some studies have also found an increased incidence of stroke with elevated blood glucose levels in nondiabetic individuals (3,4). Yet, not all studies have confirmed these findings (5,6) or have found a similar association only in women (7). Recently, a systematic overview of epidemiological studies and surveys from 52 countries found that 13% of stroke mortality cases were associated with elevated blood glucose levels measured by fasting plasma glucose (FPG) levels (4). The association between hyperglycemia and stroke events is, however, not as unequivocally described as that between hyperglycemia and coronary heart disease (CHD). The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study Group revealed that 2-h postchallenge hyperglycemia is more strongly related to CHD than fasting hyperglycemia. A similar correlation was, however, not found for stroke mortality, probably because of the low number of stroke events (8).

With an extended the follow-up and an increase in the number of participants, the number of stroke events have accumulated in the DECODE study. We have therefore now reexamined the relationship between hyperglycemia and stroke mortality and compared the difference between the 2-h and the fasting glucose criteria in prediction of stroke mortality.

RESEARCH DESIGN AND METHODS

— The study population comprised 21,706 individuals, 11,844 (55%) men and 9,862 (45%) women, from 13 European cohorts. The age range at the baseline survey was 25–90 years with mean ages varying from 45 to 76 years in different cohorts. The maximum duration of follow-up ranged from 3.8 to 27.9 years among different cohorts with a median follow-up of 10.5 years. Among the study population, 1,196 (5.5%) individuals had previously been diagnosed with diabetes. Individuals who had previously not been diagnosed as diabetic were classified according to either 2-h plasma glucose criteria (≥11.1 mmol/l for diabetes, 7.8–11.0 mmol/l for impaired glucose tolerance [IGT], and <7.8 mmol/l for normal glucose tolerance [NGT]) or FPG criteria (≥7.0 mmol/l for diabetes, 6.1–6.9 mmol/l for impaired fasting glucose [IFG], and <6.1 mmol/l for normal fasting glucose [NFG]). Measurements for 2-h plasma glucose, FPG, BMI, total serum cholesterol, systolic and diastolic blood pressure, antihypertensive treatment, and smoking status were available for each study population included in the current analysis.

Vital status and the cause of death were recorded for participants in all of the studies. Participants who had emigrated and whose vital status could not be confirmed were treated as censored cases. Ce-

From the [1]Department of Public Health, University of Helsinki, Helsinki, Finland; the [2]Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland; the [3]Institute for Research in Extramural Medicine, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; the [4]Department of Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands; [5]Imperial College, St Mary's Campus, St Mary's Hospital, London, U.K.; the [6]Department of Medicine, University of Kuopio, Kuopio, Finland; the [7]Department of Public Health/Geriatrics, Uppsala University Hospital, Uppsala, Sweden; and the [8]Department of Public Health and Clinical Medicine, University of Umeå, Umeå, Sweden.
Corresponding author: Marjukka Hyvärinen, marjukka.hyvarinen@helsinki.fi.
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Table 1—*Demographic data at baseline and number of stroke events during the follow-up in each study*

	Men	Women	Age (years)	Stroke		Maximum follow-up years
				Men	Women	
Finland, East-West*	405	—	76.2 ± 4.5	29 (7.2)	—	16.2
FINRISK-1987	1,261	1,440	54.0 ± 5.8	25 (2.0)	24 (1.7)	19.0
FINRISK-1992	877	1,041	54.1 ± 6.0	6 (0.7)	7 (0.7)	14.0
FINRISK-2002	1,786	2,055	57.9 ± 7.8	3 (0.2)	2 (1.2)	3.9
Helsinki Policemen Study*	1,136	—	44.7 ± 8.0	79 (7.0)	—	36.8
Vantaa	271	335	65.2 ± 0.4	5 (1.8)	9 (2.7)	13.9
Italy, Cremona	799	1,003	58.4 ± 10.8	5 (0.6)	2 (0.2)	6.9
The Netherlands, Hoorn Study	1,087	1,282	61.7 ± 7.3	12 (1.1)	11 (0.9)	10.2
Zuthpen Study*	479	—	75.8 ± 4.5	9 (1.9)	—	4.8
Sweden, MONICA	1,733	1,760	48.9 ± 13.4	18 (1.0)	8 (0.5)	20.6
Uppsala*	1,164	—	71.0 ± 0.6	27 (2.3)	—	12.4
U.K., Goodinge	448	570	54.6 ± 10.3	8 (1.8)	1 (0.2)	9.7
Newcastle	398	376	54.8 ± 12.5	5 (1.3)	4 (1.1)	10.6
Total	11,844	9,862	56.8 ± 11.3	231 (2.0)	68 (0.7)	36.8

Data are *n*, means ± SD, or *n* (%), unless otherwise indicated. *The study includes only men.

rebrovascular death was used as an end point and coded according to the ICD with codes 430–438 (8th and 9th revisions) and codes I60–I69 (10th revision). The methods to recruit participants for the DECODE cohorts have been described previously (8,9). Briefly, the database was collected from researchers who had performed epidemiological studies using standard 2-h 75-g oral glucose tolerance tests in Europe. Individual data from different participating European cohorts were sent to the Diabetes and Genetic Epidemiology Unit of the National Public Health Institute in Helsinki, Finland, for data analyses. Each study had been approved by the local ethics committees, and the ethics committee of the National Public Health Institute approved the data analysis plan.

Statistical methods

A general linear model of univariate ANOVA was used to estimate the means adjusted for age and center. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and their 95% CIs for stroke mortality in the different FPG and 2-h plasma glucose levels. The models were adjusted for age, center, hypertension status (≥140/90 mmHg or treatment), BMI, total serum cholesterol, smoking status, and sex. BMI was calculated as weight in kilograms divided by height in meters squared, and smoking status was classified as current smoker, exsmoker, or nonsmoker. Cumulative mortality curves were plotted using the same multivariate Cox proportional hazards analysis. χ^2 log-likelihood ratio tests were used to determine the difference between the FPG and 2-h plasma glucose criteria. SPSS (version 15; SPSS, Chicago, IL) was used for data analysis.

RESULTS — The number of participants, their demographic data at baseline, and the number of stroke events in each DECODE cohort that accumulated during the follow-up years are shown in Table 1. Mortality from stroke was higher in diabetic than in nondiabetic individuals. Individuals previously not diagnosed as diabetic with 2-h plasma glucose levels ≥11.1 mmol/l or FPG levels ≥7.0 mmol/l were older and had higher BMI and cholesterol levels than individuals with 2-h plasma glucose <11.1 mmol/l or FPG <7.0 mmol/l. Similar results were found in both men and women (Table 2).

The multivariate-adjusted HR for fatal stroke events was highest in men with screen-detected diabetes defined by 2-h plasma glucose criteria as compared with men with NGT or IGT. A significant increase in HRs was seen in women with screen-detected diabetes defined by either FPG or 2-h plasma glucose criteria as compared with women with NFG or NGT (Table 2). The cumulative hazards were highest in people with previously diagnosed diabetes and screen-detected diabetes defined by both criteria (Fig. 1*A–B* and Fig. 2*A–B*); the risk was moderately increased for IFG in women (Fig. 1*B*) and for IGT in men (Fig. 2*A*). The risk of fatal stroke events was lowest in men with NFG or IFG (Fig. 1*A*) and in women with NGT or IGT (Fig. 2*B*). Thus, the classification based on 2-h plasma glucose better discriminated fatal stroke events in men, whereas that based on FPG was a better predictor in women.

The HRs corresponding to a 1-SD increase in 2-h plasma glucose or FPG are shown in Table 3. The log-likelihood ratio test showed that addition of 2-h plasma glucose to the model with FPG significantly improved the prediction of the model ($\chi^2 = 10.45$; $P = 0.001$) in all individuals and in men ($\chi^2 = 10.12$; $P = 0.001$) but not in women ($\chi^2 = 0.01$; $P = 0.94$). Addition of FPG to the model with 2-h plasma glucose improved the prediction of stroke mortality in women but not in men (Table 3). Interaction of sex with FPG was found to be significant ($P = 0.05$) but not with 2-h plasma glucose ($P = 0.53$).

Because waist circumference and triglycerides were not measured in all cohorts included in the current data analysis, they were not adjusted in the final model. Their effects were, however, tested in a subgroup of 9,010 (42%) men and 8,900 (41%) women with measurement of waist and a subgroup of 10,379 (48%) men and 8,235 (38%) women with triglycerides. Adjustment for either waist or triglycerides did not change the results for 2-h plasma glucose in men or FPG in women, but it attenuated the hazards for 2-h plasma glucose in women and FPG in men. The HRs adjusting for waist corresponding to a 1-SD increase in 2-h plasma glucose were 1.23 (95% CI 0.99–1.52) in men and 1.07 (0.78–1.48) in women; those corresponding to a 1-SD increase in FPG were 1.08 (0.86–1.35) in men and 1.38 (0.95–2.00) in women. HRs adjust-

Table 2—*Baseline characteristics and multivariate adjusted HR (95% CI) for death from stroke for subjects according to FPG and 2-h plasma glucose categories*

	FPG			2-h plasma glucose			
	<6.1	6.1–6.9	≥7.0	<7.8	7.8–11.0	≥11.1	Known diabetes
Men							
n (%)	8,540 (72.1)	2,043 (17.2)	537 (4.5)	9,065 (76.5)	1,558 (13.2)	497 (4.2)	724 (6.1)
Age (years)	56.9 ± 0.1	57.2 ± 0.3	62.4 ± 0.5	55.8 ± 0.1	63.2 ± 0.3	65.1 ± 0.5	62.8 ± 0.4
BMI (kg/m^2)	26.3 ± 0.0	27.4 ± 0.1	29.0 ± 0.2	26.3 ± 0.0	27.7 ± 0.1	28.9 ± 0.2	28.3 ± 0.1
Cholesterol (mmol/l)	6.04 ± 0.01	6.09 ± 0.03	6.11 ± 0.05	6.07 ± 0.01	5.99 ± 0.03	6.04 ± 0.05	5.78 ± 0.04
SBP (mmHg)	140 ± 0.2	145 ± 0.4	148 ± 0.9	140 ± 0.2	147 ± 0.5	151 ± 0.9	145 ± 0.7
DBP (mmHg)	83 ± 0.1	85 ± 0.3	87 ± 0.5	83 ± 0.1	86 ± 0.3	87 ± 0.5	84 ± 0.4
Smoking	2,507 (29.4)	637 (31.2)	157 (29.2)	2,835 (31.3)	360 (23.1)	106 (21.3)	166 (22.9)
Stroke							
n (%)	141 (1.7)	45 (2.2)	15 (2.8)	153 (1.7)	35 (2.2)	13 (2.6)	30 (4.1)
n per 1,000 person-years	1.46	1.90	3.24	1.43	2.47	3.50	5.57
HR (95% CI)	1	1.05 (0.74–1.49)	1.37 (0.79–2.38)	1	1.43 (0.97–2.11)	1.82 (1.01–3.29)	3.32 (2.16–5.12)
Women							
n (%)	8,169 (82.8)	969 (9.8)	252 (2.6)	7,766 (78.7)	1,281 (13.0)	343 (3.5)	472 (4.8)
Age (years)	54.9 ± 0.1	59.0 ± 0.3	61.1 ± 0.6	54.5 ± 0.1	59.6 ± 0.3	62.4 ± 0.5	60.8 ± 0.5
BMI (kg/m^2)	26.5 ± 0.1	28.6 ± 0.2	30.6 ± 0.3	26.4 ± 0.1	28.6 ± 0.1	30.0 ± 0.3	30.1 ± 0.2
Cholesterol (mmol/l)	6.22 ± 0.01	6.27 ± 0.04	6.32 ± 0.07	6.22 ± 0.01	6.27 ± 0.03	6.21 ± 0.06	5.86 ± 0.05
SBP (mmHg)	137 ± 0.2	141 ± 0.7	143 ± 1.3	137 ± 0.2	144 ± 0.6	147 ± 1.1	147 ± 1.0
DBP (mmHg)	80 ± 0.1	81 ± 0.4	82 ± 0.7	80 ± 0.1	83 ± 0.3	84 ± 0.6	81 ± 0.5
Smoking	1,650 (20.2)	237 (24.5)	67 (26.6)	1,712 (22.0)	184 (14.4)	58 (16.9)	67 (14.2)
Stroke							
n (%)	37 (0.5)	10 (1.0)	7 (2.8)	36 (0.5)	9 (0.7)	9 (2.6)	14 (3.0)
n per 1,000 person-years	0.44	1.25	3.35	0.46	0.72	3.03	3.93
HR (95% CI)	1	2.04 (0.99–4.21)	4.73 (2.00–11.18)	1	0.90 (0.43–1.90)	3.33 (1.55–7.14)	5.60 (2.86–10.96)
Total							
n (%)	16,709 (77.0)	3,012 (13.9)	789 (3.6)	16,831 (77.5)	2,839 (13.1)	840 (3.9)	1,196 (5.5)
Age (years)	56.0 ± 0.1	57.6 ± 0.2	61.8 ± 0.4	55.2 ± 0.1	61.6 ± 0.2	63.9 ± 0.4	61.9 ± 0.3
BMI (kg/m^2)	26.4 ± 0.0	27.9 ± 0.1	29.5 ± 0.1	26.4 ± 0.0	28.1 ± 0.1	29.3 ± 0.1	29.1 ± 0.1
Cholesterol (mmol/l)	6.12 ± 0.01	6.20 ± 0.02	6.20 ± 0.04	6.14 ± 0.01	6.11 ± 0.02	6.12 ± 0.04	5.83 ± 0.03
SBP (mmHg)	139 ± 0.2	144 ± 0.4	146 ± 0.7	138 ± 0.2	145 ± 0.4	149 ± 0.7	146 ± 0.6
DBP (mmHg)	82 ± 0.1	83 ± 0.2	85 ± 0.4	82 ± 0.1	85 ± 0.2	86 ± 0.4	82 ± 0.3
Smoking	4,157 (24.9)	874 (29.0)	224 (28.4)	4547 (27)	544 (19.2)	164 (19.5)	233 (19.5)
Stroke							
n (%)	178 (1.1)	55 (1.8)	22 (2.8)	189 (1.1)	44 (1.5)	22 (2.6)	44 (3.7)
n per 1,000 person-years	0.98	1.74	3.27	1.02	1.65	3.29	4.92
HR (95% CI)	1	1.19 (0.87–1.64)	1.83 (1.16–2.89)	1	1.30 (0.92–1.84)	2.31 (1.46–3.67)	3.85 (2.68–5.53)

Data are *n* (%) and means ± SE unless otherwise indicated. Data are adjusted for age, study, and sex (when men and women combined). FPG and 2-h plasma glucose criteria are in mmol/l. DBP, diastolic blood pressure; SBP, systolic blood pressure.

ing for triglycerides were for 2-h plasma glucose 1.24 (1.03–1.50) in men and 0.98 (0.65–1.49) in women, whereas for FPG 0.87 (0.69–1.10) and 1.50 (0.90–2.48), respectively. Further adjustment for either waist or triglycerides in the subgroups did not change the main results based on the whole study population.

CONCLUSIONS — We confirmed in this analysis that diabetes defined by either FPG or 2-h plasma glucose criteria conveyed increased stroke mortality. Individuals with IFG defined according to the FPG criteria alone had a stroke mortality lower than those with diabetes but higher than those with NFG in women but not in men, whereas the opposite was found for IGT and NGT. Stroke mortality was higher in men with IGT than in men with NGT, but such a difference was not seen in women.

Overt diabetes (1,10) as well as diabetes defined based on 1-h postload glucose (11), FPG levels (12,13), or nonfasting glucose levels (7,14) have been reported to predict an increased risk of stroke. Yet, studies that have conducted a 2-h oral glucose tolerance test and compared the stroke risk between 2-h postload hyperglycemia and fasting hyperglycemia are rare. Moreover, because the category IFG has only recently been introduced (15), studies estimating the stroke risk in individuals with IFG compared with those with IGT are very few. The DECODE Study Group (8) previously found that the risk of stroke death was higher in women with IFG than with IGT (8), but as a result of the low number of stroke deaths, a direct comparison between FPG and 2-h plasma glucose was not made separately for men and women. With the increasing number of stroke deaths accumulated in the DECODE cohorts, the glucose-stroke relationship was reinvestigated in detail in the present data analysis. With regard to CHD mortality,

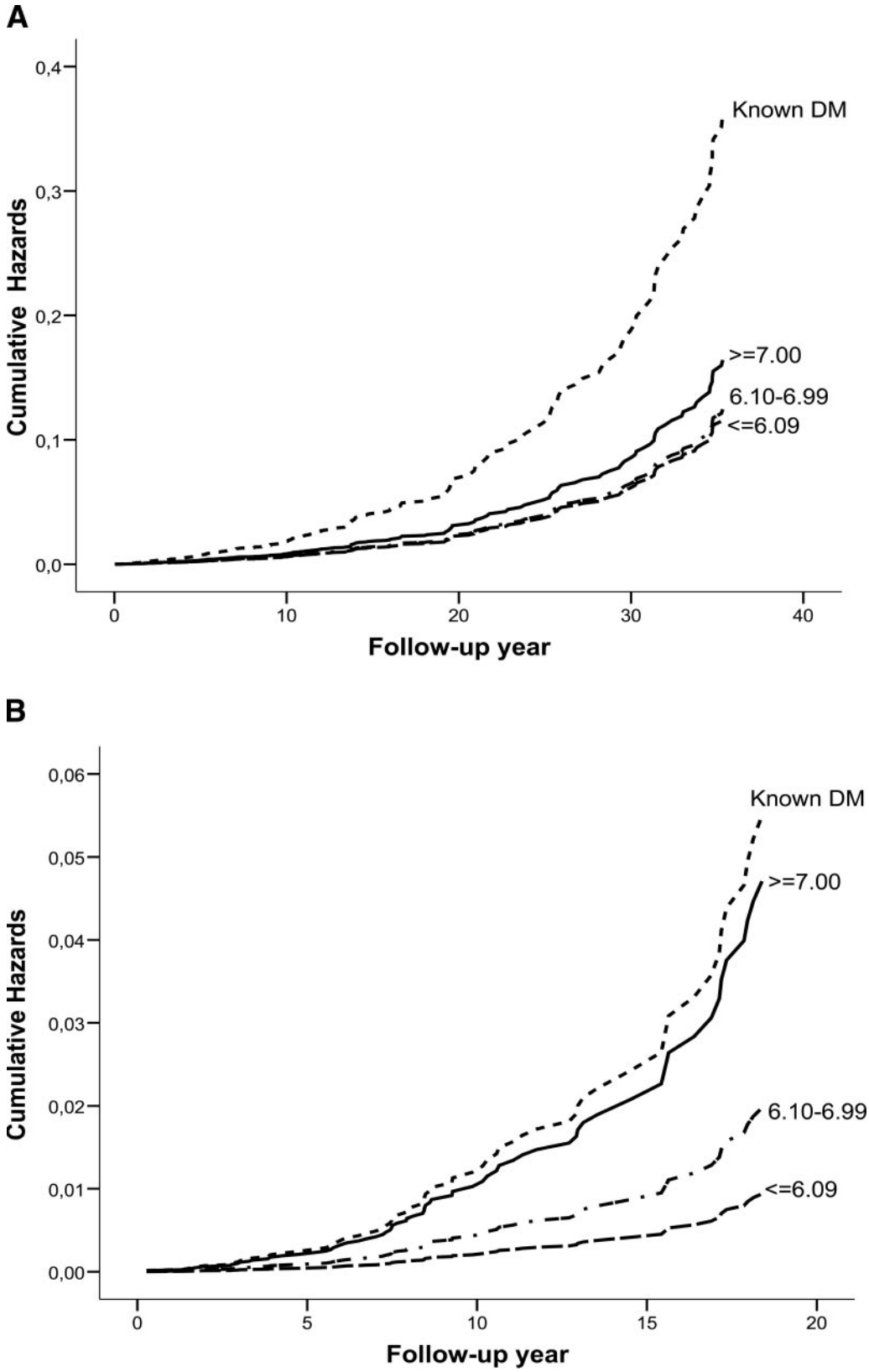

Figure 1—*Cumulative stroke mortality curves derived from Cox regression analysis for FPG (mmol/l) and for people with prior history of diabetes (known DM) in men* (A) *and in women* (B)*. The analysis is adjusted for age, study, BMI, total cholesterol, smoking, and hypertension status.*

when we analyzed the data with men and women together, the findings of the present study (results not shown) were in accordance with the previous findings (8). Also, in the present study, when men and women were pooled, the 2-h plasma glucose–stroke relation was still stronger than the FPG-stroke relation. However, when the data were analyzed separately,

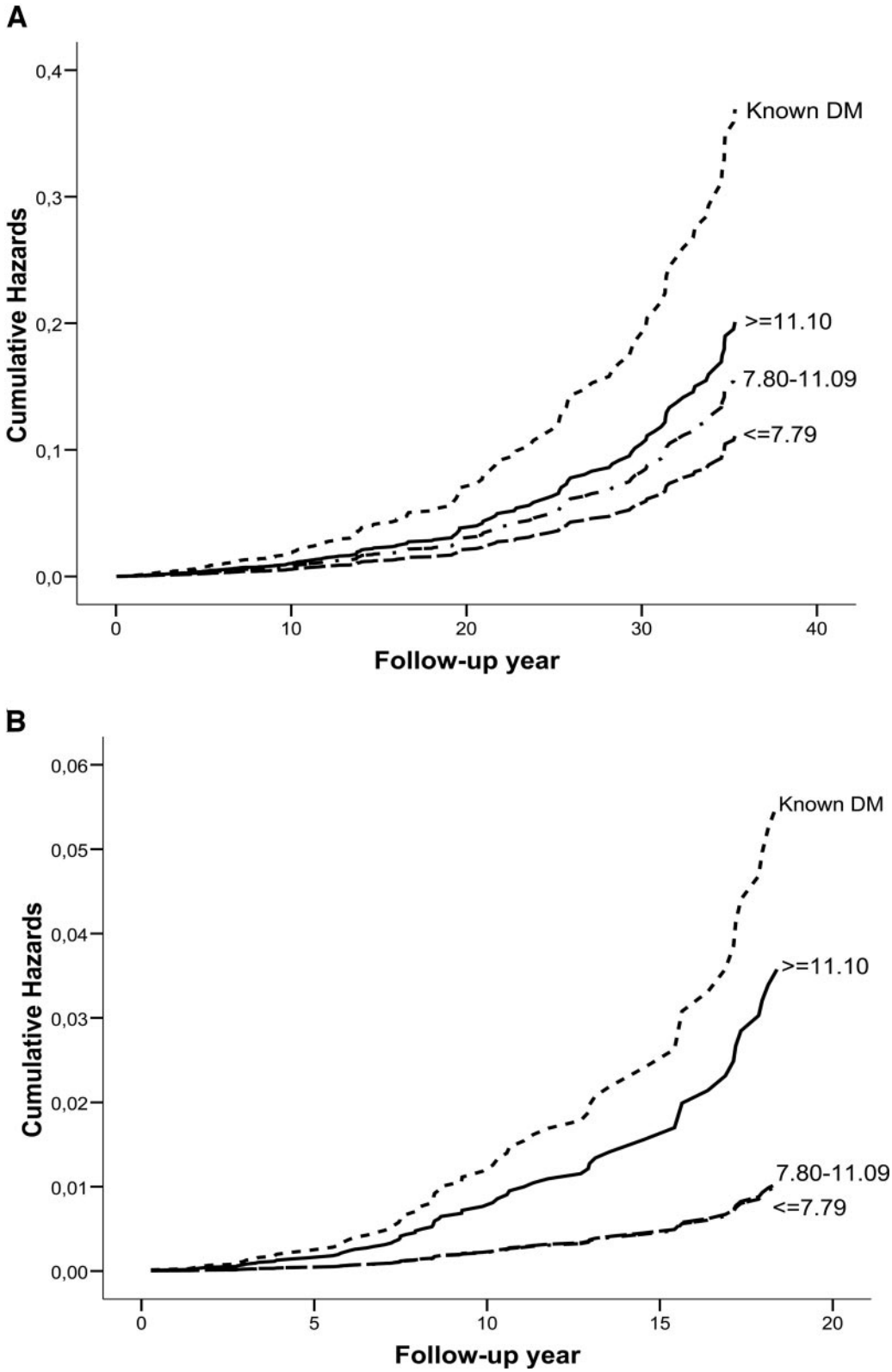

Figure 2—*Cumulative stroke mortality curves derived from Cox regression analysis for 2-h plasma glucose (mmol/l) and for people with prior history of diabetes (known DM) in men* (A) *and in women* (B)*. The analysis is adjusted for age, study, BMI, total cholesterol, smoking, and hypertension status.*

we found that in men, the 2-h plasma glucose criteria better predicted stroke mortality than the FPG criteria, but in women the role was reversed. When the data are analyzed with men and women together, the majority of the stroke deaths come from men, and the results of the men drive the direction of the analysis; thus, the sex differences in FPG and 2-h plasma

Table 3—*HR (95% CI) for death from stroke corresponding to a 1-SD increase in FPG or 2-h plasma glucose levels fitted in the model separately*

	Adjustment*	Men	Women	Total
n		11,120	9,390	20,510
Model 1†	Age, study, BMI, total cholesterol			
FPG		1.04 (0.85–1.27)	1.54 (1.26–1.90)	1.18 (1.03–1.35)
2-h plasma glucose		1.21 (1.06–1.38)	1.31 (1.07–1.61)	1.25 (1.12–1.40)
Model 2†	Model 1 + smoking			
FPG		1.04 (0.86–1.27)	1.56 (1.26–1.92)	1.27 (1.14–1.42)
2-h plasma glucose		1.23 (1.08–1.40)	1.34 (1.09–1.65)	1.18 (1.03–1.36)
Model 3†	Model 2 + hypertension			
FPG		1.02 (0.83–1.25)	1.52 (1.22–1.88)	1.16 (1.00–1.33)
2-h plasma glucose		1.21 (1.06–1.38)	1.31 (1.06–1.61)	1.25 (1.12–1.40)
χ^2 for FPG, 1 df (*P*)		3.29 (0.07)	4.08 (0.04)	0.57 (0.45)
χ^2 for 2-h PG, 1 df (*P*)		10.12 (0.001)	0.01 (0.94)	10.45 (0.001)

χ^2 indicates the changes in the model prediction when FPG or 2-hPG was removed from the model where both were fitted simultaneously. Subjects with diagnosed diabetes were excluded. *Adjusted for sex when men and women are combined. †SD = 1.3 for FPG and SD = 2.7 for 2-h plasma glucose.

glucose criteria with regard to stroke risk remain undetected.

Diabetes increases the risk of CHD events (16).The risk is more markedly increased in diabetic women than in diabetic men (17). This was also found in the current study population of all ages: the ratio of male CHD mortality to female CHD mortality in subjects with normal glucose levels (both NFG and NGT) and with diabetes (diagnosed or undiagnosed) was 5.94 and 2.53, respectively.

The underlying pathophysiologies of IFG and IGT are different. IFG is predominantly associated with hepatic insulin resistance and decreased first-phase insulin secretion, whereas IGT is associated with peripheral insulin resistance and impairment of both early- and late-phase insulin responses (18). A population study in Mauritius reported that men have lower levels of β-cell function and higher prevalence of IFG than women and women have lower insulin sensitivity and higher prevalence of IGT than men (19). Thus, the stroke mortality in relation to the two glucose categories may also differ between the two sexes, which could partly explain the differences found between men and women in the present study.

Abdominal adiposity, measured as waist circumference or as waist-to-hip ratio, has been found to increase the risk of ischemic stroke in both men and women (20) or in men only (21). Plasma triglyceride levels have also been shown to have an association with increased risk of stroke in some (22) but not all studies (23) or have been found to have an increased stroke risk only in women (24). Because the two variables, waist circumference and triglycerides, were not measured in all of the cohorts used in the present study, adjustments for these variables were not done in the final data analysis. However, when their effect was tested in a subgroup of individuals, the results did not change, indicating that the 2-h plasma glucose category improves the prediction of stroke mortality in men compared with FPG category alone, whereas the latter is better than the former in women.

Overt diabetes is more closely related to ischemic stroke than to hemorrhagic stroke (25). Regardless of the relatively large sample size, the follow-up duration for many of the cohorts in the present study is still short, with few stroke events accumulated, and as a result of the small number of stroke events in women, we could not further classify people into ischemic or hemorrhagic stroke. This is one of the limitations of the current study. In addition, in the DECODE study, some cohorts included men only, and thus cohorts for men and women in the present analysis were to some extent different. One may speculate that the sex-specific glucose-stroke relationship is study-dependent. However, when we limit the data analysis to the studies comprising both men and women, the results were not changed. The strength of the present study is that all the cohorts used in the study had data available for both FPG and 2-h glucose levels. This is the first study to investigate the question of glucose levels and the risk of stroke in a study group where all participants had a 2-h 75-g oral glucose tolerance test. The collaborative data analysis gives more statistical power than if the analysis had been performed individually by the different centers, and thus avoids the spurious results caused by a small study. To try to take into account the difference between studies, in all pooled data analysis, "cohort" was adjusted for.

In summary, the present study confirmed that diabetes defined by either fasting or postchallenge criteria is a predictor of stroke mortality in both sexes. In people without diabetes, elevated 2-h postchallenge glucose is a better predictor than elevated fasting glucose in men, whereas fasting plasma glucose is better than 2-h postchallenge glucose in women.

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