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ARTICLE

The effect of diabetes and stroke at baseline and during follow-up on stroke mortality

G. Hu · P. Jousilahti · C. Sarti · R. Antikainen · J. Tuomilehto

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Abstract
Aims/hypothesis The aim of this study was to compare the magnitude of the effect of diabetes and stroke at baseline and during follow-up on risk of stroke mortality.
Materials and methods Study cohorts included 25,155 Finnish men and 26,423 women aged 25–74 years. Data on diabetes and stroke history at baseline, their incidence during follow-up, and stroke death were obtained from national registers.
Results During a mean follow-up of 18.9 years, 838 stroke deaths were recorded. In the baseline study, hazard ratios (HRs) for stroke mortality were 5.26 for men with prior diabetes only, 4.76 for men with prior stroke only, and 13.4 for men with both prior diabetes and stroke compared with men without diabetes and stroke at baseline and during follow-up. In women, the corresponding hazard ratios were 7.29, 5.27 and 5.52, respectively. When only diabetes and stroke status during the follow-up were considered, the hazard ratios for stroke mortality were 1.41 for men and 1.56 for women with incident diabetes only, 5.62 for men and 5.58 for women with incident stroke only, and 5.59 for men and 4.48 for women with both incident diabetes and stroke compared with men and women without diabetes and stroke at baseline and during follow-up.
Conclusions/interpretation Diabetes and stroke, present either at baseline or during follow-up, markedly increase the risk of stroke death. Prior stroke at baseline carries a similar risk of stroke mortality as prior diabetes. There is a greater risk of stroke mortality associated with incident stroke during follow-up than with incident diabetes.

Keywords Mortality · Stroke · Type 2 diabetes

Abbreviations

CVD	cardiovascular disease
HR	hazard ratio
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease

G. Hu · P. Jousilahti · C. Sarti · J. Tuomilehto
Department of Epidemiology and Health Promotion,
National Public Health Institute,
Helsinki, Finland

G. Hu · C. Sarti · J. Tuomilehto
Department of Public Health, University of Helsinki,
Helsinki, Finland

P. Jousilahti
School of Public Health, University of Tampere,
Tampere, Finland

R. Antikainen
Oulu City Hospital and Department of Internal Medicine,
Oulu University,
Oulu, Finland

J. Tuomilehto
South Ostrobothnia Central Hospital,
Seinäjoki, Finland

G. Hu (✉)
Diabetes and Genetic Epidemiology Unit,
Department of Epidemiology and Health Promotion,
National Public Health Institute,
Mannerheimintie 166,
FIN-00300 Helsinki, Finland
e-mail: hu.gang@ktl.fi

Introduction

Type 2 diabetes is one of the fastest growing public health problems worldwide as a result of increasing obesity and a sedentary lifestyle. The number of diabetic patients in the

world has been estimated to at least double over the next 30 years [1]. Cardiovascular disease (CVD) accounts for more than 75% of total mortality among patients with type 2 diabetes [2–4]. Epidemiological studies have indicated that the risk of CVD mortality is two to four times higher in patients with type 2 diabetes than in those without diabetes [5]. Recent studies have investigated whether a history of myocardial infarction has the same risk on coronary death as a history of type 2 diabetes [6–13]. Our previous study reported that, among men, those who experienced myocardial infarction at baseline or during follow-up were at greater risk of coronary mortality than those with prior or incident diabetes; in women, prior myocardial infarction at baseline was associated with a lower risk of coronary mortality than prior diabetes, but incident myocardial infarction during follow-up was associated with a greater risk than incident diabetes [13]. Several prospective studies have assessed the independent effect of type 2 diabetes on stroke risk, with inconsistent results. Some [14–22], but not all studies [23, 24], have identified type 2 diabetes as an independent risk factor for stroke. Moreover, it is not fully understood whether the risk of stroke death associated with incident diabetes is similar to that associated with incident stroke. The aim of this study was to compare the magnitude of the effect of diabetes and stroke at baseline and during follow-up on the risk of stroke mortality.

Subjects and methods

Subjects

Six independent cross-sectional population surveys were carried out in Kuopio and North Karelia provinces in eastern Finland in 1972, 1977, 1982, 1987, 1992 and 1997 [25]. The survey areas were expanded to Turku-Loimaa region in southwestern Finland in 1982, the Helsinki capital area in 1992, and the northern province of Oulu in 1997. In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample has been stratified by area, sex and age (10-year groups) according to the World Health Organization Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) protocol [26]. In six surveys, the subjects included were 25–64 years of age, and, in the 1997 survey, subjects aged 65–74 years were also included. Subjects were recruited by six independent surveys, and subjects who participated in more than one survey were included in the first survey cohort only. The total sample size of the six surveys was 53,166. The participation rate varied by year from 74 to 88% [25]. After excluding 113 subjects with type 1 diabetes at baseline or during follow-up, 1,204 subjects with incomplete data on any required variable, and 271 patients who died within 28 days of the diagnosis date of incident diabetes or stroke during follow-up, the present analyses included 25,155 men and 26,423 women. The participants gave informed consent (verbal 1972–1992 and signed 1997). These surveys were conducted according to the ethics rules of the National Public Health Institute and the investigations were carried out in accordance with the Declaration of Helsinki.

Measurements

A self-administered questionnaire was mailed to the participants. This included questions about smoking, socioeconomic factors, alcohol consumption, physical activity and medical history. Based on the responses, the participants were classified as never, ex- and current-smokers. Years of education were divided into birth cohort-specific tertiles. Since questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the latter surveys, the participants were categorised as either abstainers or alcohol users. Physical activity included occupational, commuting and leisure-time physical activity, and results were merged and regrouped into three categories: low, moderate and high [27–34]. At the study site, specially trained research nurses measured blood pressure, height and weight using a standardised protocol [26]. Blood pressure was measured using a standard mercury manometer after 5 min of rest. Height was measured without shoes. Weight was measured with light clothing. BMI was calculated as weight in kilograms divided by the square of height in metres. After blood pressure measurement, a venous blood specimen was drawn. Total cholesterol concentration was determined using the Lieberman Burchard method in 1972 and 1977 [35], and an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany) in 1982 onwards. Because the enzymatic method gave 2.4% lower values than the Lieberman Burchard method, 1972 and 1977 values were corrected by this percentage. All samples were analysed in the same laboratory at the National Public Health Institute.

Assessment of diabetes and stroke at baseline and during follow-up

Assessment of diabetes and stroke status was based on self-reporting and on the data of two nationwide registers. The National Hospital Discharge Register data included information on hospital discharge diagnosis from 1968 through the end of 2002. The validity of the diagnosis of stroke in Finland from this register is good [36, 37]. Data on diabetes medication were obtained from the National Social Insurance Institution's register on special reimbursement for

glucose-lowering drugs from 1964 through the end of 2002. Glucose-lowering drugs prescribed by a physician are free of charge in Finland and are subject to approval of a physician who reviews each case history. The physician confirms the diagnosis of diabetes by applying the World Health Organization criteria [38, 39]. All patients receiving free medication (either oral glucose-lowering agents or insulin) are entered into a register maintained by the National Social Insurance Institution.

Subjects who reported having diabetes on the questionnaire, or who had had a hospital discharge diagnosis of diabetes, or the approval for free-of-charge medication for diabetes before the baseline survey were classified as having prior diabetes at baseline. The subjects with prior stroke at baseline were those who reported having stroke on the questionnaire, or had a hospital discharge diagnosis of stroke before the baseline survey.

Subjects who had the first hospital discharge diagnosis with diabetes, or the approval for free-of-charge medication for diabetes after the baseline survey were classified as having incident diabetes during follow-up. Subjects with incident stroke during follow-up comprised those who had a hospital discharge with a diagnosis of stroke after the baseline survey. The patients who died within 28 days of the diagnosis date of incident diabetes and stroke during follow-up were excluded from the analysis, thus eliminating the deaths directly due to stroke.

Prospective follow-up

The study cohorts were followed until the end of 2003 through computerised register linkage using the personal identification number assigned for every resident in Finland. Mortality data were obtained from Statistics Finland. The International Classification of Diseases (ICD), Eighth, Ninth and Tenth Revisions, were used for coding the causes of death; ICD codes 430–438 and I60–I66 were classified as stroke deaths. During a mean follow-up of 18.9 years, 838 stroke deaths were recorded.

Statistics

SPSS for Windows 13.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Cox proportional hazard models were used to estimate the hazard ratios for stroke mortality associated with diabetes and stroke status. Subjects who did not have a history of stroke or prevalent diabetes at baseline and who did not develop either of the two conditions during follow-up were used as the reference group. We carried out two analyses: the baseline cohort analysis included the reference group and the patients with prior diabetes or stroke at baseline, and the follow-up cohort analysis included the reference group and the patients with incident (diagnosed after the baseline survey) diabetes or stroke during follow-up. The analyses were first carried out adjusting for age and study year, and were further adjusted for BMI, systolic blood pressure, total cholesterol, education, alcohol drinking, physical activity and smoking at baseline. A likelihood ratio test for interaction was carried out to test whether the effect of disease status on stroke mortality differed between men and women. The risk of stroke mortality associated with diabetes was compared with that associated with stroke, both at baseline and during the follow-up, using Cox regression. Age and person-years of follow-up were also calculated at the date of new diagnosis of diabetes or stroke during follow-up. A p value of less than 0.05 was considered statistically significant and all p values are two-sided.

Results

Baseline cohort study

Baseline characteristics and multivariate-adjusted (age, study year, BMI, systolic blood pressure, cholesterol, education, alcohol drinking, physical activity and smoking) hazard ratios for stroke mortality according to history of diabetes and stroke at baseline are presented in Table 1. Compared with men without diabetes and stroke at baseline and during follow-up, the multivariate-adjusted hazard ratios for stroke mortality were 5.26 (95% CI: 3.59–7.71) for men with prior diabetes only, 4.76 (95% CI: 3.02–7.49) for men with prior stroke only, and 13.4 (95% CI: 5.99–30.1) for men with both prior diabetes and stroke at baseline. In women, the corresponding HRs were 7.29 (95% CI: 4.93–10.8), 5.27 (95% CI: 3.21–8.64) and 5.52 (95% CI: 1.32–23.0), respectively. The number of women with both prior diabetes and stroke at baseline was only 23, two of whom died due to stroke, and therefore the risk estimate in this category was unreliable.

Patients with incident diabetes and/or stroke during follow-up

When diabetes and stroke status during follow-up were included in the analyses, the multivariate-adjusted hazard ratios for stroke mortality were 1.41 (95% CI: 0.96–2.09) for men and 1.56 (95% CI: 1.12–2.16) for women with incident diabetes only, 5.62 (95% CI: 4.46–7.09) for men and 5.58 (95% CI: 4.34–7.19) for women with incident stroke only, and 5.59 (95% CI: 3.55–8.81) for men and 4.48 (95% CI: 2.92–6.90) for women with both incident diabetes and stroke compared with men and women without diabetes and stroke at baseline and during the follow-up

Table 1 Baseline characteristics and hazard ratios for stroke mortality according to history of diabetes and stroke at baseline

	Men				Women			
	No diabetes and no stroke[a]	Prior diabetes and no stroke	No diabetes and prior stroke	Prior diabetes and stroke	No diabetes and no stroke[a]	Prior diabetes and no stroke	No diabetes and prior stroke	Prior diabetes and stroke
Number of subjects	21,559	542	401	53	23,227	490	271	23
Age at baseline (years)	43.7±11.5	53.4±10.6	55.3±10.2	59.2±9.1	43.8±11.3	52.9±10.9	56.2±9.1	58.3±9.4
BMI (kg/m^2)	26.0±3.5	28.4±4.5	27.8±3.9	28.5±4.0	25.6±4.5	29.8±6.0	28.3±5.1	30.8±6.8
Diastolic blood pressure (mm Hg)	87±12	89±14	91±12	90±15	83±12	88±13	88±12	90±16
Systolic blood pressure (mm Hg)	142±18	151±23	150±22	156±24	137±22	152±25	150±24	159±31
Serum cholesterol (mmol/l)	6.1±1.2	6.1±1.4	6.3±1.3	6.3±1.2	6.0±1.3	6.3±1.4	6.5±1.3	6.5±1.5
Education (years)	9.4±3.9	8.2±3.9	7.6±3.6	8.4±4.8	9.8±3.9	7.8±3.8	7.8±3.3	6.1±2.4
Alcohol drinker (%)	65.5	56.5	46.9	49.1	36.8	22.9	21.4	17.4
Low physical activity (%)	7.1	18.8	28.2	28.3	9.0	30.0	32.8	52.2
Current smoking (%)	42.0	35.6	37.7	22.6	17.5	13.9	12.5	4.3
Number of stroke deaths	188	36	24	7	174	34	19	2
Person-years	388,746	7,060	4,728	475	451,351	7,109	3,945	313
Age- and study year-adjusted HR (95% CI)	1.00	6.48 (4.50–9.34)	6.74 (4.36–10.4)	22.1 (10.2–48.1)	1.00	8.93 (6.10–13.1)	6.27 (3.85–10.2)	9.37 (2.29–38.3)
Multivariate-adjusted HR (95% CI)[b]	1.00	5.26 (3.59–7.71)	4.76 (3.02–7.49)	13.4 (5.99–30.1)	1.00	7.29 (4.93–10.8)	5.27 (3.21–8.64)	5.52 (1.32–23.0)

Baseline characteristics are presented as means±SD or percentages.
[a]No diabetes and no stroke included disease status at baseline and during follow-up
[b] Adjusted for age, study year, BMI, systolic blood pressure, total cholesterol, education, alcohol drinking, physical activity and smoking

(Table 2). Sex and disease status did not interact with each other to have a significant effect on stroke mortality, either at baseline or at follow-up.

Comparison of stroke mortality between diabetes and stroke at baseline and during follow-up

When stroke mortality in persons with prior diabetes only was compared with that in persons with a history of stroke only at baseline, men and women with prior stroke showed almost the same risk of stroke mortality as men (hazard ratio [HR]=0.97, 95% CI: 0.57–1.67) and women (HR=0.75, 95% CI: 0.42–1.33) with prior diabetes, after adjustment for all confounding factors (Fig. 1). When stroke mortality was compared between persons who developed diabetes during follow-up and those who experienced stroke only, men and women with incident stroke had significantly higher multivariate-adjusted hazard ratios of stroke mortality (HR=4.07, 95% CI: 2.67–6.21 in men; HR=3.53, 95% CI: 2.45–5.09 in women) than men and women with incident diabetes (Fig. 2). When age and person-years of follow-up were calculated at the date of diagnosis of incident diabetes or incident stroke during follow-up, the multivariate-adjusted hazard ratios for stroke

Table 2 Baseline characteristics and hazard ratios for stroke mortality according to incident diabetes and stroke during follow-up

	Men				Women			
	No diabetes and no stroke[a]	Incident diabetes and no stroke	No diabetes and incident stroke	Incident diabetes and stroke	No diabetes and no stroke[a]	Incident diabetes and no stroke	No diabetes and incident stroke	Incident diabetes and stroke
Number of subjects	21,559	1,328	1,103	169	23,227	1,343	882	187
Age at baseline (years)	43.7±11.5	45.7±10.3	50.5±10.4	50.4±10.3	43.8±11.3	49.6±9.6	51.7±9.5	53.4±8.0
BMI (kg/m^2)	26.0±3.5	29.2±4.3	26.7±3.4	29.2±3.9	25.6±4.5	30.9±5.7	27.1±4.6	31.0±5.3
Diastolic blood pressure (mm Hg)	87±12	94±13	91±12	94±12	83±12	93±13	90±12	95±13
Systolic blood pressure (mm Hg)	142±18	149±20	150±21	152±23	137±22	156±26	151±24	162±27
Serum cholesterol (mmol/l)	6.1±1.2	6.5±13	6.6±1.3	6.7±1.2	6.0±1.3	6.6±1.4	6.7±1.4	6.7±1.2
Education (years)	9.4±3.9	8.2±3.4	7.5±3.4	7.2±3.2	9.8±3.9	7.2±3.1	7.6±3.3	6.4±2.8
Alcohol drinker (%)	65.5	63.0	61.5	54.4	36.8	19.3	23.6	16.0
Low physical activity (%)	7.1	11.1	10.1	13.0	9.0	19.4	15.1	21.9
Current smoking (%)	42.0	45.5	47.3	41.4	17.5	13.7	14.7	9.1
Number of stroke deaths	188	31	126	22	174	51	99	25
Person-years	388,746	28,973	22,444	3,718	451,351	31,525	19,788	4,238
Age- and study year-adjusted HR (95% CI)	1.00	1.62 (1.11–2.37)	6.14 (4.87–7.73)	6.25 (4.01–9.75)	1.00	2.09 (1.52–2.86)	5.77 (4.49–7.42)	5.85 (3.83–8.93)
Multivariate-adjusted HR (95% CI)[b]	1.00	1.41 (0.96–2.09)	5.62 (4.46–7.09)	5.59 (3.55–8.81)	1.00	1.56 (1.12–2.16)	5.58 (4.34–7.19)	4.48 (2.92–6.90)

Baseline characteristics are presented as means±SD or percentages.

[a]No diabetes and no stroke included disease status at baseline and during follow-up

[b]Adjusted for age, study year, body mass index, systolic blood pressure, total cholesterol, education, alcohol drinking, physical activity and smoking

mortality were 4.03 (95% CI: 2.65–6.14) for men and 4.06 (95% CI: 2.80–5.88) for women with incident stroke compared with men and women with incident diabetes.

Discussion

In both sexes, a history of diabetes and stroke at baseline and incident diabetes and stroke during follow-up markedly increased the risk of stroke mortality. Subjects with a history of stroke at baseline were at the same risk of stroke mortality as those with a history of diabetes at baseline. When disease status during follow-up was considered, subjects with incident stroke had a higher risk of stroke mortality than those with incident diabetes.

Coronary heart disease has been identified as the leading cause of death among patients with type 2 diabetes [2]. In recent years, several studies have compared the magnitude of the risk of a history of type 2 diabetes and myocardial infarction on subsequent coronary mortality [6–13]. A Finnish prospective study found that the risk of coronary death among diabetic subjects without prior myocardial infarction was similar to that in non-diabetic subjects with prior myocardial infarction [6], but this finding has been challenged by several later studies [8–13]. The Health Professionals' Follow-up Study and the Atherosclerosis

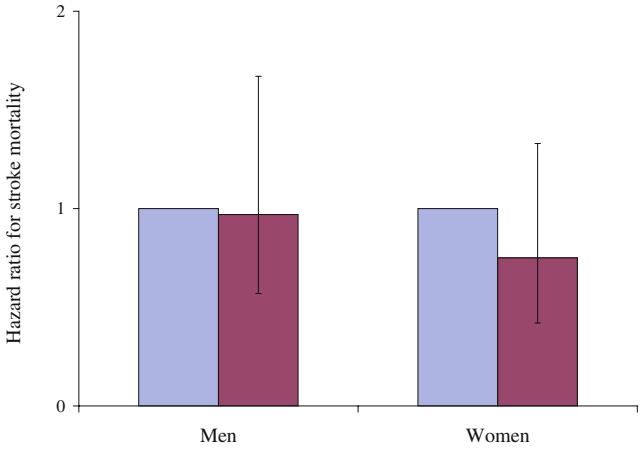

Fig. 1 Hazard ratios for stroke mortality in diabetic subjects without a history of stroke as compared with non-diabetic subjects with a history of stroke at baseline. Adjusted for age, study year, BMI, systolic blood pressure, total cholesterol, education, alcohol drinking, physical activity and smoking. *Blue bars*, prior diabetes; *red bars*, prior stroke

Risk in Communities Study reported that the magnitude for coronary or cardiovascular mortality was lesser for diabetes than that associated with prior myocardial infarction [7, 10]. The analyses of data from the Finland Cardiovascular Risk (FINRISK) study revealed that, among men, the risk of coronary mortality is greater in those with myocardial infarction at baseline or during follow-up than in those with diabetes. In women, however, prior myocardial infarction at baseline confers a lower risk of coronary mortality than prior diabetes does, but incident myocardial infarction during follow-up confers a greater risk than incident diabetes does [13].

Several studies have recently assessed the relationship between type 2 diabetes and the risk of stroke. Type 2 diabetes has been shown to be an independent risk factor for stroke morbidity [15, 18–22] and mortality [14, 16, 17, 22, 40]. The Renfrew and Paisley Study found that type 2 diabetes was a predictor of stroke incidence among women but not among men [41]. The Dubbo Study in the Australian elderly failed to confirm prediction of incident ischemic stroke by diabetes [24]. Moreover, several studies have found that subjects with impaired fasting glucose levels have an increased risk of stroke [3, 20, 42, 43].

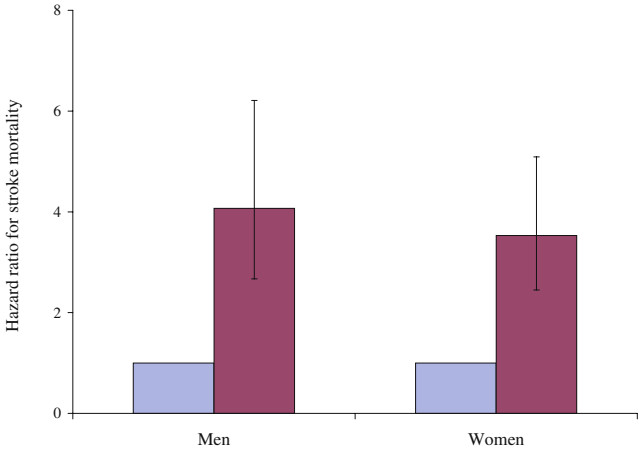

Fig. 2 Hazard ratios for stroke mortality in diabetic subjects without stroke as compared with non-diabetic subjects with stroke during follow-up. Adjusted for age, study year, BMI, systolic blood pressure, total cholesterol, education, alcohol drinking, physical activity and smoking. *Blue bars*, incident diabetes; *red bars*, incident stroke

However, whether the risk of stroke death associated with a history of stroke is similar to that associated with a history of type 2 diabetes is not fully understood. The Women's Pooling Project, which included nine prospective epidemiological studies, was the only study to compare the magnitude of the risk of stroke mortality in subjects with a history of diabetes at baseline with that in subjects with a history of stroke [40], using the same design as our baseline cohort study. The results indicated that the risk of fatal stroke in diabetic subjects without stroke was similar to that in non-diabetic subjects with a history of stroke. However, this observational study analysed a single baseline measurement. In the present study, prior stroke at baseline was associated with almost the same risk of stroke mortality as prior diabetes at baseline, whereas in the follow-up study, incident stoke was associated with a higher risk of stroke mortality than incident diabetes. The results were almost similar in men and women. The magnitude of the effect of diabetes and stroke on stroke risk probably depends on the duration of the disease, and this time factor may operate differently for diabetes than for stroke. Among the patients who have survived an acute stroke, the risk of subsequent stroke event is highest immediately after the attack and the risk stabilizes over time, whereas among diabetic subjects, the stroke risk increases with the duration of the disease [15]. As in the baseline cohort analyses of our study, most previous studies have not paid attention to the time of stroke event or duration of diabetes in their data analyses.

The definition of type 2 diabetes is different between these previous studies and our study. In most observational prospective studies, diabetes status is usually recorded only once at baseline [14, 15, 17–21, 24, 40, 41]. Subjects who develop diabetes later are considered non-diabetic, or an unexposed reference group. This misclassification causes an underestimation of the diabetes-related risk of stroke. In our study, patients with newly diagnosed diabetes during follow-up had a 40–60% higher risk of stroke death, and patients with both diabetes and stroke newly diagnosed during follow-up had a 4.5–5.6 fold risk of stroke death compared with subjects who were free of diabetes and stroke both at baseline and during the follow-up.

Our finding may have some important implications for the minimising stroke risk in diabetic patients, because a history of diabetes has the same stroke risk as a history of prior stroke. Better management and prevention of diabetes

are needed. The UKPDS demonstrated the importance of maintaining good glycaemic control for prevention of the development and progression of complications among patients with type 2 diabetes [44]. Clinical trials have shown that pharmacological treatment of hypertension [45–47] and cholesterol reduction with a statin therapy [42, 43, 48–50] are efficient ways of preventing stroke and other cardiovascular events in patients with diabetes or impaired fasting glucose.

Our study has several strengths and limitations. We have the unique possibility of stratifying for both baseline and follow-up status of diabetes and stroke. There are a large number of participants from a homogeneous population. The mean follow-up was sufficiently long to ascertain a large number of stroke endpoint events. We excluded the subjects with type 1 diabetes from the analysis, and, due to computerized data linkage of national mortality data, endpoint data collection was practically complete. A limitation of our study was that we did not carry out either a fasting glucose test or a glucose tolerance test at baseline or at follow-up. We would therefore have failed to identify cases of asymptomatic or diet-treated diabetes, especially among those patients who were diagnosed with stroke at baseline or during follow-up, although the clinical diagnosis of diabetes in the hospital discharge register included a proportion of those not using drugs, reducing this potential under-diagnosis. Thus, we cannot completely exclude the bias due to the above limitation. However, the total prevalence of type 2 diabetes at baseline and during follow-up in the present study was 8.1%, which is almost the same as the prevalence of this Finnish population according to a survey with an oral glucose tolerance test [51]. Another limitation of our study was that we did not have data on the severity of the diabetes or stroke, glycaemic control, or the type of drug treatment used for diabetes, stroke and other chronic diseases.

In conclusion, we have compared the independent effects of diabetes and stroke at baseline and during follow-up on the risk of stroke mortality. Diabetes and stroke, either present at baseline or during follow-up, markedly increase the risk of stroke death. Prior stroke at baseline has the same risk on stroke mortality as prior diabetes. There is a greater risk of stroke mortality associated with incident stroke during follow-up than with incident diabetes.

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