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ARTICLE

Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database

H. E. Mulnier · H. E. Seaman · V. S. Raleigh · S. S. Soedamah-Muthu · H. M. Colhoun · R. A. Lawrenson · C. S. De Vries

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Abstract
Aims/hypothesis Risk estimates for stroke in patients with diabetes vary. We sought to obtain reliable risk estimates for stroke and the association with diabetes, comorbidity and lifestyle in a large cohort of type 2 diabetic patients in the UK.
Materials and methods Using the General Practice Research Database, we identified all patients who had type 2 diabetes and were aged 35 to 89 years on 1 January 1992. We also identified five comparison subjects without diabetes and of the same age and sex. Hazard ratios (HRs) for stroke between January 1992 and October 1999 were calculated, and the association with age, sex, body mass index, smoking, hypertension, atrial fibrillation and duration of diabetes was investigated.
Results The absolute rate of stroke was 11.91 per 1,000 person-years (95% CI 11.41–12.43) in people with diabetes (n=41,799) and 5.55 per 1,000 person-years (95% CI 5.40–5.70) in the comparison group (n=202,733). The age-adjusted HR for stroke in type 2 diabetic compared with non-diabetic subjects was 2.19 (95% CI 2.09–2.32) overall, 2.08 (95% CI 1.94–2.24) in men and 2.32 (95% CI 2.16–2.49) in women. The increase in risk attributable to diabetes was highest among young women (HR 8.18; 95% CI 4.31–15.51) and decreased with age. No investigated comorbidity or lifestyle characteristic emerged as a major contributor to risk of stroke.
Conclusions/interpretation This study provides risk estimates for stroke for an unselected population from UK general practice. Patients with type 2 diabetes were at an increased risk of stroke, which decreased with age and was higher in women. Additional risk factors for stroke in type 2 diabetic patients included duration of diabetes, smoking, obesity, atrial fibrillation and hypertension.

Keywords Database · Primary care · Risk · Risk factors · Stroke · Type 2 diabetes

Abbreviations

GPRD	General Practice Research Database
HR	hazard ratio

H. E. Mulnier (✉) · H. E. Seaman · V. S. Raleigh · R. A. Lawrenson · C. S. De Vries
Department of Pharmacoepidemiology, Postgraduate Medical School, University of Surrey, Daphne Jackson Road, Manor Park, Guildford, Surrey GU2 7WG, UK
e-mail: h.mulnier@surrey.ac.uk

V. S. Raleigh
Healthcare Commission, London, UK

S. S. Soedamah-Muthu · H. M. Colhoun
Department of Epidemiology and Public Health, Royal Free and University College London Medical School, London, UK

S. S. Soedamah-Muthu
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

H. M. Colhoun
Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

R. A. Lawrenson
Waikato Clinical School, University of Auckland, Auckland, New Zealand

Introduction

Although 20% of strokes may be associated with diabetes [1], published risk estimates for stroke associated with diabetes vary from no increased risk [2] to a more than sixfold increase in risk [3]. The increase in risk attributable to diabetes appears to decrease with increasing age [2, 4–6]. Indeed, Wong et al. showed that after the age of 75 years, patients with diabetes had the same risk of stroke as those without diabetes [2]. The evidence for an increase in risk with smoking and obesity in people with diabetes is conflicting [3, 7–13].

Part of the variation in the published risk estimates for stroke in people with diabetes may be explained by the composition of the study populations [2, 3, 9, 14]. Many studies excluded older patients, did not differentiate between diabetes type, selected from a population that had a different underlying risk of stroke from that of the UK or used the general population containing diabetes as the comparison group [9, 10, 13, 14]. This study sought to obtain reliable risk estimates for stroke across all age-groups in a cohort of over 40,000 people with type 2 diabetes and over 200,000 without diabetes, and to test the effect of sex, BMI, smoking habits, hypertension, atrial fibrillation and duration of diabetes.

Subjects and methods

Study population A cohort study was conducted using data from the General Practice Research Database (GPRD). The GPRD provides anonymised data from general practices across the UK for some 5% of the population, and includes data on demographics, diagnoses and symptoms, prescriptions and hospital admissions. Information on people's lifestyles such as smoking habit is also available. GPRD data have been shown to be of high quality and validity, and have been used extensively for epidemiological studies [15–21].

From the GPRD we identified, in practices contributing research quality data, all individuals aged 35 to 89 on 1 January 1992 (baseline). Patients with type 2 diabetes were identified using an algorithm based on age at diagnosis and type of treatment. Full details of the cohort selection have been published elsewhere [22–24]. For each patient with type 2 diabetes five comparison subjects of the same age and sex and with no record of or treatment for diabetes at any time before 1992 or during the follow-up period were selected at random from the database.

Identifying stroke Individuals with a record of stroke were identified blind to whether the patient had or did not have diabetes. Algorithms were established to identify and assess the reliability of new stroke diagnoses recorded after baseline. The diagnosis was considered 'definite' where a stroke was recorded and the patient died within 30 days or where there was evidence of relevant prescribing (aspirin, warfarin, dipyridamole or clopidogrel) plus other supporting evidence of stroke (hospital discharge, physiotherapy or rehabilitation, confirmation of stroke by computed tomography, EEG) within 60 days. 'Probable' strokes had a record of stroke and relevant prescribing or supporting evidence, but not both. If only a stroke record was evident, these were considered 'possible' strokes. To ensure that limb weaknesses due to cardiovascular causes only were included, patients with cancer or a new diagnosis of multiple sclerosis were excluded from the analysis. Individuals with a record of stroke before baseline were excluded from the study population.

Lifestyle factors and comorbidity BMI was calculated using available height and weight recordings closest to baseline. Patient records were reviewed to confirm apparent BMIs of <20 kg/m^2 or >50 kg/m^2. Calculated BMIs of <15 or >55 kg/m^2 (<1% of final calculations) were deemed unreliable and the patient's BMI status was coded as 'unknown'. Similarly, smoking status was defined by records closest to baseline, a method described by Hubbard et al. [25]. Smoking records may refer to the number of cigarettes smoked per day or to smoking habit, e.g. non-smoker, smoker. If the record closest to baseline was 'non-smoker' but a 'smoker' record existed earlier, the patient's smoking status was coded as 'ex-smoker'. Among patients with diabetes, duration of diabetes at baseline was estimated either from the date of the first diabetes record or the date of the first diabetes-related prescription, whichever was earlier. All patients with a record of hypertension and/or atrial fibrillation before baseline were identified using appropriate codes.

Statistical analysis Analyses were performed using STATA version 8 (STATA, College Station, TX, USA). Cox proportional hazards models were used. Rates of stroke were calculated for patients with diabetes and the comparison group by age-group and sex, using the number of events divided by the number of person-years at risk that were contributed by each group. Multivariate analyses were carried out in the diabetes cohort, adjusting for sex, duration of diabetes, smoking, BMI, atrial fibrillation and hypertension, and then stratified by age and sex. Where the date of diagnosis was unreliable (3.1%), the average duration of diabetes in that age-group was assumed for the multivariate analysis. To allow for change in age-group across the 7-year study period, all age-grouping was performed using Lexis expansion. Sensitivity analyses were carried out to test the reliability of stroke diagnosis and the

impact of missing data. We checked for interaction between risk factors and the effect of using risk factor data at baseline. Further analyses were performed using different age and BMI-grouping to allow direct comparison with other published risk estimates and rates of stroke.

Ethical permission was given for this study by the GPRD Scientific and Ethical Advisory Group.

Results

We identified 985 definite, 1,102 probable and 568 possible new strokes among 41,799 patients with type 2 diabetes and 2,374, 2,609 and 1,404, respectively, in the comparison group (n=202,733). Sensitivity analyses revealed that the reliability of diagnosis had no effect on risk estimates. When a random sample of patient records from the definite and probable categories was viewed, no evidence disputing the diagnosis of stroke was found. The reported analyses are based upon the definite and probable strokes (78.2% of all strokes). Population characteristics are provided in Table 1. The proportion of missing BMI and smoking data was high, especially in the comparison group.

The absolute rate of stroke was 11.91 per 1,000 person-years (95% CI 11.41–12.43) in the cohort with diabetes (Table 2) and 5.55 per 1,000 person-years (95% CI 5.40–5.70) in the comparison group (Table 3). In the diabetes group, 34.5% died within 28 days of the stroke record, compared with 36.3% in the comparison group. The overall age-adjusted HR for stroke in type 2 diabetes compared with those without diabetes was 2.19 (95% CI 2.09–2.32)

Table 1 Characteristics of the study cohort at baseline and percentage with stroke during the study

	Type 2 diabetes				Comparison group			
	Men	Percentage (%)	Women	Percentage (%)	Men	Percentage (%)	Women	Percentage (%)
Total	22,178	53.1	19,621	46.9	107,285	52.9	95,448	47.1
Age (years)								
35–44	962	4.3	643	3.3	4,801	4.5	3,212	3.4
45–54	3,038	13.7	1,852	9.4	15,105	14.1	9,220	9.7
55–64	6,079	27.4	4,390	22.4	29,920	27.9	21,759	22.8
65–74	7,076	31.9	6,076	31.0	34,148	31.8	29,708	31.1
75–84	4,369	19.7	5,380	27.4	20,321	18.9	25,615	26.8
≥85	654	2.9	1,280	6.5	2,990	2.8	5,934	6.2
Average age in 1992 (years)	65		68		65		68	
Smoking status								
Current smoker	4,443	20.0	2,440	12.4	21,608	20.1	12,740	13.3
Ex-smoker	2,177	9.8	981	5.0	8,786	8.2	4,043	4.2
Non-smoker	12,240	55.2	12,610	64.3	45,889	42.8	50,954	53.4
Unknown smoking status	3,318	15.0	3,590	18.3	31,002	28.9	27,711	29.0
Atrial fibrillation	840	3.8	840	4.3	2,325	2.2	2,023	2.1
Hypertension	6,233	28.1	7,492	38.2	16,060	15.0	19,375	20.3
Duration of diabetes (years)								
0–4	11,059	49.9	9,762	49.8	NA		NA	
5–9	5,183	23.4	4,691	23.9	NA		NA	
10–14	2,613	11.8	2,407	12.3	NA		NA	
≥15	2,632	11.9	2,151	11.0	NA		NA	
Unknown duration of diabetes	691	3.1	610	3.1	NA		NA	
BMI (kg/m^2)								
15–19	211	1.0	395	2.0	1,637	1.5	2,879	3.0
20–24	4,189	18.9	3,073	15.7	20,666	19.3	20,402	21.4
25–29	8,086	36.5	4,925	25.1	29,380	27.4	20,033	21.0
30–34	3,153	14.2	3,131	16.0	6,915	6.4	6,771	7.1
≥35	955	4.3	2,000	10.2	1,160	1.1	2,459	2.6
Unknown BMI	5,584	25.2	6,097	31.1	47,527	44.3	42,904	45.0
Definite stroke after baseline	438	2.0	547	2.8	1,094	1.0	1,280	1.3
Probable stroke after baseline	575	2.6	527	2.7	1,393	1.3	1,216	1.3
Possible stroke after baseline	301	1.4	267	1.4	723	0.7	681	0.7

Table 2 Number of stroke events and rates per 1,000 person-years by sex and attained age-group in patients with type 2 diabetes

	Events (*n*)		Person-years at risk		Rate/1,000 person-years (95% CI)		
	Men	Women	Men	Women	All	Men	Women
Age (years)							
35–44	5	3	2,758	1,964	1.69 (0.85–3.39)	1.81 (0.76–4.36)	1.53 (0.49–4.74)
45–54	31	22	11,547	7,361	2.80 (2.14–3.67)	2.69 (1.89–3.82)	3.00 (1.97–4.54)
55–64	149	99	25,268	17,510	5.80 (5.12–6.57)	6.00 (5.02–6.92)	5.65 (4.64–6.89)
65–74	368	278	31,486	25,984	11.24 (10.41–12.14)	11.69 (10.55–12.95)	10.80 (9.51–12.03)
75–84	355	462	18,869	22,255	19.87 (18.55–21.28)	18.81 (16.96–20.88)	20.76 (18.95–22.74)
≥85	105	210	3,704	6,523	30.80 (27.58–34.40)	28.35 (23.42–34.33)	32.20 (28.12–36.86)
All ages	1,013	1,074	93,631	81,597	11.91 (11.41–12.43)	10.82 (10.17–11.51)	13.16 (12.40–13.97)

overall, 2.08 (95% CI 1.94–2.24) in men and 2.32 (95% CI 2.16–2.49) in women (Table 4). The risk of stroke attributable to diabetes was most marked among young women (HR 8.18; 95% CI 4.31–15.51). The diabetes-associated risk decreased with age and was higher in women across all age groups.

Table 5 demonstrates the risk estimates for stroke associated with co-morbidity and lifestyle factors among people with and without diabetes. The unadjusted risk of stroke was significantly higher for men in the comparison group, but not in the diabetes group (HR 0.99; 95% CI 0.91–1.08). The increased risk associated with hypertension and atrial fibrillation appeared less marked in the diabetes group than in the comparison group. The risk for those with type 2 diabetes who had stopped smoking was not different from the risk among current smokers with type 2 diabetes. An increase in risk for stroke associated with obesity was seen only in those with a BMI >35 kg/m^2 in the diabetes cohort. The results of the multivariate analysis among people with diabetes showed little change in any of the HRs compared with the univariate analyses, suggesting that these risk factors are independent.

Sensitivity analyses excluding or including unknown BMI or smoking as separate groups made no difference to the HRs for known BMI and smoking. Further analyses assigning unknown BMI by age-group to average, mode, below average and very obese did not alter the HRs significantly. No interactions were found between diabetes and any of the other risk factors. To test whether the use of risk factor data collected closest to baseline affected the risk estimates, we repeated the analysis first with follow-up ending 1 year from baseline and then in those with data continuing beyond 1997. The risk estimates were largely unchanged. Multivariate analysis stratified by age-group and sex showed no significant change in the risk estimates for BMI, smoking habits, hypertension or atrial fibrillation in any age-group or either sex.

Discussion

This study demonstrated that type 2 diabetes is associated with a twofold increase in the risk of stroke, but there was no difference in 28-day case fatality compared with patients without diabetes. This is consistent with other smaller studies [1, 2, 5, 26–28]. The increase in risk associated with diabetes decreased with age and was highest in young women (HR 8.18 [95% CI 4.31–15.51]). This was not explained by a higher frequency of obesity, smoking or comorbidity in this subpopulation. Men with type 2 diabetes were at the same risk of stroke as their female

Table 3 Number of stroke events and rates per 1,000 person-years by sex and attained age-group in patients without type 2 diabetes

	Events (*n*)		Person-years at risk		Rate/1,000 person-years (95% CI)		
	Men	Women	Men	Women	All	Men	Women
Age (years)							
35–44	3	2	14,027	9,750	0.21 (0.09–0.51)	0.21 (0.07–0.66)	0.21 (0.05–0.82)
45–54	36	13	58,280	36,031	0.52 (0.39–0.69)	0.62 (0.45–0.86)	0.36 (0.21–0.62)
55–64	224	102	125,643	87,928	1.53 (1.37–1.70)	1.78 (1.56–2.03)	1.16 (0.96–1.41)
65–74	791	513	158,412	135,432	4.44 (4.20–4.69)	5.00 (4.66–5.35)	3.79 (3.47–4.13)
75–84	1,084	1,176	97,101	118,616	10.48 (10.05–10.92)	11.16 (10.52–11.85)	9.91 (9.36–10.50)
≥85	349	690	19,674	37,233	18.26 (17.18–19.40)	17.74 (15.97–19.70)	18.53 (17.20–19.69)
All ages	2,487	2,496	473,138	424,990	5.55 (5.40–5.70)	5.26 (5.05–5.47)	5.87 (5.65–6.12)

Table 4 Hazard ratios (95% CI) for stroke in diabetes compared with no diabetes stratified by sex and attained age-group

	All	Men	Women
Diabetes/no diabetes (*n*)	41,799/ 202,733	22,178/ 107,285	19,621/ 95,448
Age (years)			
35–54	5.64 (3.91–8.13)	4.66 (2.96–7.33)	8.18 (4.31–15.51)
55–64	3.81 (3.23–4.49)	3.31 (2.69–4.07)	4.89 (3.71–6.45)
65–74	2.54 (2.31–2.79)	2.35 (2.07–2.65)	2.83 (2.45–3.28)
75–84	1.90 (1.75–2.06)	1.69 (1.49–1.90)	2.10 (1.89–2.34)
≥85	1.69 (1.49–1.92)	1.60 (1.28–1.99)	1.74 (1.49–2.03)
All ages	2.19 (2.09–2.32)	2.08 (1.94–2.24)	2.32 (2.16–2.49)

counterparts (HR 0.91 [95% CI 0.91–1.08]). This has also been demonstrated in previous studies [1–3, 8, 14, 29, 30].

The risk associated with obesity in people with diabetes was increased only in the group with a BMI >35 kg/m^2, reflecting perhaps the lack of association between stroke and obesity seen in other smaller studies among people with diabetes [3, 9, 11–13]. Using BMI <23 kg/m^2 as the reference and grouping as in the Physicians' Health Study [10], where the study population included individuals with diabetes, our study showed a smaller non-significant increase in risk; those with a BMI >30 kg/m^2 had a 40% increased risk compared with 112% in that study (data not shown). Although the Physicians' Health Study showed obesity to be an independent risk factor for stroke, our study suggests that weight loss may be of benefit only in the very obese with type 2 diabetes. The absence of difference in risk between smokers and ex-smokers among people with type 2 diabetes is consistent with work by Tuomilehto et al. [13] and suggests that smoking cessation may have little impact on risk of stroke in people with type 2 diabetes, although smoking cessation has many other known health benefits. Even though patients with diabetes were twice as likely to have a diagnosis of atrial fibrillation or hypertension, the associated increase in risk of stroke was small and significantly less than that in patients without diabetes. None of the individual variables measured in our analysis appeared to explain the elevated risk of stroke in diabetes.

Unlike studies where the general population is used as the comparison, our comparison group had no record of diabetes prior to baseline or at any time during follow-up. It has been estimated that a person may have undiagnosed

Table 5 Hazard ratios (95% CI) for risk factors in people with diabetes and people without diabetes

	Unadjusted univariate analyses, diabetes cohort (*n*=41,799)[a]	Unadjusted univariate analyses, non-diabetic comparison group (*n*=202,733)[a]	Multivariate analyses, diabetes cohort (*n*=41,799)[b]
Men : women	0.99 (0.91–1.08)	1.19 (1.13–1.26)	1.02 (0.93–1.12)
Duration (years)			
0–4	Reference	Reference	Reference
5–9	1.29 (1.16–1.43)	NA	1.29 (1.17–1.43)
10–14	1.21 (1.06–1.39)	NA	1.22 (1.07–1.40)
≥15	1.42 (1.25–1.61)	NA	1.47 (1.29–1.67)
Smoking status			
Non-smoker	Reference	Reference	Reference
Current smoker	1.29 (1.14–1.46)	1.45 (1.34–1.58)	1.36 (1.20–1.55)
Ex-smoker	1.26 (1.07–1.48)	1.15 (1.02–1.29)	1.29 (1.10–1.52)
Unknown smoking status	1.46 (1.31–1.65)	1.14 (1.06–1.21)	1.38 (1.20–1.58)
BMI (kg/m^2)			
15–19	0.82 (0.56–1.21)	1.20 (1.01–1.43)	0.81 (0.55–1.20)
20–24	Reference	Reference	Reference
25–29	0.98 (0.86–1.12)	0.99 (0.91–1.09)	0.98 (0.86–1.12)
30–34	1.15 (0.98–1.34)	1.22 (1.08–1.39)	1.15 (0.98–1.34)
≥35	1.36 (1.12–1.67)	1.03 (0.80–1.33)	1.36 (1.11–1.67)
Unknown BMI	1.33 (1.17–1.51)	1.23 (1.14–1.33)	1.21 (1.05–1.39)
Atrial fibrillation	1.56 (1.32–1.85)	2.36 (2.12–2.64)	1.59 (1.34–1.88)
Hypertension	1.28 (1.17–1.40)	1.52 (1.43–1.61)	1.30 (1.19–1.42)

Calculated in separate univariate analyses for people with and without diabetes, and also in a multivariate analysis for the type 2 diabetes group.
[a] Correcting for current age
[b] Correcting for current age, sex, duration, BMI, atrial fibrillation and hypertension

type 2 diabetes for between 4 and 7 years before diagnosis [31]. In our study population, the maximum follow-up period from baseline was 7.9 years and the average was 4.4 years. While we are confident that the burden of undiagnosed diabetes in our comparison group is likely to be low, we cannot ignore the possibility that any undiagnosed diabetes in the comparison group could attenuate the observed differences in risk.

Our findings are subject to some limitations. Although the inclusion of patients with unknown BMI and smoking data made no difference to the HRs, we accept that missing data will have resulted in residual confounding, and risk estimates associated with BMI should therefore be interpreted with caution. However, sensitivity analyses did not give cause for concern. In addition, with regard to the risk associated with obesity, if waist circumference had been available this might have proven to be a more reliable predictor of stroke in type 2 diabetic patients. The duration data show that the majority of patients had a duration of diabetes of less than 5 years. This may be a result of the retrospective recording of diagnosis in those diagnosed with diabetes before the patient's registration on the database, resulting in a possible underestimation of diabetes duration. Unfortunately, because of the nature of onset in type 2 diabetes and the likelihood of a period of undiagnosed diabetes, determining the duration of type 2 diabetes in a study such as this is always subject to limitations. Misclassification of stroke may have led to underestimated risks, but there is no reason to believe that this will have been differential between the diabetes and comparison groups, as stroke status was assessed blind to diabetes status. Records with hypertension or atrial fibrillation prior to baseline may have been missed if not coded by the general practitioner. Again, however, those with codes were identified blind to the diabetes status.

Patients with type 2 diabetes tend to be elderly and are managed principally in primary care. It is therefore appropriate to derive risk estimates from data collected from general practice. The validity of the diagnostic data is important and GPRD data have been used in previous studies to estimate the prevalence of diabetes [32] and the incidence of stroke [33–35]. Our data using supporting evidence to confirm diagnosis among 80% of patients with a stroke code also agree with that of a previous GPRD cerebrovascular disease validation study [34]. We have also compared our rates of stroke in the comparison group without diabetes with that of the Oxford Vascular Study [36], and those in the diabetes group with those published by McAlpine et al. [37], and the findings are remarkably consistent. Thus although we acknowledge that a database study such as this is limited in as far as the study population is not a true inception cohort, we believe that the data from this study are reliable and can be generalised to the UK.

Conclusions

The data from this study provide risk estimates for stroke from an unselected population with type 2 diabetes in the UK compared with a non-diabetic population. The risk associated with diabetes was highest in young women and although this risk decreased with age, patients aged over 75 years were still at increased risk. Our analysis confirmed a significantly increased risk of stroke associated with hypertension, atrial fibrillation and high BMI, although, despite a twofold increase in the prevalence of these risk factors among patients with type 2 diabetes, the risk estimates for stroke associated with these known risk factors did not differ significantly between patients with diabetes and those without. The results highlight the need for detection and treatment of diabetes particularly in the young and in women; they also highlight the burden of comorbidity in diabetes on a population basis.

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