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Incidence Of Stroke in People with Diabetes Compared to Those Without Diabetes: A Systematic Review

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Abstract

The aim of our review was to evaluate the incidence of stroke in the diabetic population and its differences regarding sex, ethnicities, age and regions, to compare the incidence rate (IR) in people with and without diabetes, and to investigate time trends.

A systematic review was conducted according to the guidelines for meta-analysis of observational studies in epidemiology (the MOOSE group) and to the PRISMA 2020 group guidelines. Nineteen of the 6.470 studies retrieved were included in the analysis. The age-sex standardized incidence rate of stroke in the population with diabetes ranged from 238 per 100,000 person-years (PYs) in Germany in 2014 to 1191 during the 1990s in the United Kingdom (UK). The relative risk (RR) comparing people with diabetes to those without diabetes varied between 1.0 and 2.84 for total stroke, 1.0 and 3.7 for ischemic stroke, and 0.68 and 1.6 for hemorrhagic stroke. Significant differences were found between fatal and non-fatal stroke depending on the time period and the population. We found decreasing time trends in people with diabetes and stable incidence rates of stroke over time in people without diabetes. The considerable differences between results can partly be explained by differences in study designs, statistical methods, definitions of stroke, and methods used to identify patients with diabetes. The lack of evidence arising from these differences ought to be rectified by new studies.

Keywords: *Population-based study, time trends, fatal and non-fatal stroke, diabetes mellitus.*

Introduction

The prevalence of diabetes mellitus (DM) has increased substantially. According to the International Diabetes Federation, the estimated prevalence of diabetes (type 1 and type 2 combined) in people aged 20–79 years has risen from 151 million (4.6% of the global population) in 2000 to 463 million (9.3%) in 2019 [1]. This increase has led to an increasing number of people with diabetic micro- and macrovascular complications, including stroke [2]. In addition, stroke is a major cause of disability and death worldwide [3]. It is not only crucial to reduce the incidence of stroke to improve quality of life, but also to mitigate the economic consequences associated with stroke (high costs due to hospitalizations, rehabilitation, and social-services support). However, only few epidemiological studies have assessed time trends of stroke incidence comparing people with and without diabetes [4-7] The St. Vincent Declaration set the goal of reducing the incidence of stroke among people with diabetes to match the incidence in those without diabetes [8]. However, it remains uncertain as to whether this goal has been achieved.

Previous systematic reviews have investigated diabetes as a risk factor for stroke [9-14]. Several studies identified marked differences in incidence and RR of stroke in people with diabetes compared to the population without diabetes [15-17]. Published data are contradictory and heterogeneous in their definitions and recordings of diabetes, the methods used to count and describe stroke

events, and their definitions of the population at risk. Furthermore, statistical methods often differ between the studies because some estimated age-sex standardized IRs while others solely reported crude rates. Finally, knowledge is limited regarding the extent to which differences between people with and without diabetes are considered when evaluating types of strokes, i.e. ischemic, hemorrhagic, fatal or non-fatal strokes to better guide stroke prevention and control programs.

The main objectives of this systematic review were (a) to evaluate and compare the incidence of stroke in people with and without diabetes, (b) to detect differences between the incidences of various stroke types (all types, ischemic, hemorrhagic, fatal, non-fatal) with respect to sex, age and ethnicity, and (c) to investigate time trends.

Material and methods

This systematic review was conducted according to a predetermined protocol and established guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA/PRISMA-P [18,19]. A study protocol with the registration number CRD42017073159 was published [20]

Search strategy and selection criteria

We conducted a systematic search in the literature databases MEDLINE, Embase and LILACS from inception to April 2021. This database selection corresponds with the recommendations for searching for epidemiological studies [21]. A comprehensive search strategy was developed by an experienced information scientist and tested against eight known relevant references from previous systematic reviews according to the guidelines for meta-analysis of observational studies in epidemiology (the MOOSE group) [22]. The search strategy for all databases can be found in supplementary material. The retrieved records were exported into EndNote and duplicates were removed manually.

We aimed to identify further potentially eligible studies by using additional methods, such as checking reference lists of review articles and relevant studies. We contacted the authors of those studies for which we could not obtain the full text despite our efforts of making use of interlibrary loan.

Types of studies and populations

All population-based longitudinal studies which used prospective and retrospective designs to analyze IRs of stroke among people with and without diabetes and reported RRs and time trends were included in this review. The source population (population at risk) had to be defined by official statistics (e. g., nationwide data or all residents of a specific region) or statutory health insurance institutions (e. g., all people insuredby a statutory health insurance institution). Individuals with diabetes (incident or prevalent) had to be identified or diagnosed in a valid manner, i.e. the diabetes diagnosis had to be clearly described (e.g., documented in medical records, self-reported or physician-diagnosed diabetes, intake of antihyperglycemic medication, or as an HbA1c value).

Studies were excluded if: (a) they solely reported the incidence of stroke among persons with diabetes without comparison to people without diabetes; (b) IRs were reported in relation to the total population and not exclusively using the population with diabetes as the population at risk; (c) only crude IRs were reported. Given the assumed profound heterogenity of included studies based on prior experience with comparable systematic reviews [23,24], no meta-analysis was planned.

Data extraction

The main outcome incidence of stroke was analyzed according to clinical diagnoses of ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SCH), all types of strokes, and survival (non-fatal/fatal/both). We extracted the IR (per 100,000 PYs with 95% confidence intervals (95% CI)) or cumulative incidence (CumI) of stroke. To compare IRs of the populations with and without diabetes the RR, the hazard ratio (HR) or incidence rate ratio (IRR) was considered depending on what publications reported. Where available, time trends and differences in the stroke risk associated with demographic variables (sex, ethnicity, age) and regions were extracted. All presented results (IR, RR, HR, IRR) were standardized or adjusted for age and sex. Furthermore, study-related data such as study design, study period, data source and reporting methods for stroke, and patient-related data such as age range, gender, data sources for diabetes and for stroke were extracted.

Quality assessment and risk of bias

The quality of eligible studies was assessed by two independent reviewers, considering the studies´ limitations and risk of bias using a modified checklist as per the Methodological Evaluation of Observational Research (MORE) [25], Scottish Intercollegiate Guidelines Network (SIGN) [26], and the Cochrane Approach Study Quality Guide [27]. These tools were used to define criteria based on clinical and epidemiological expertise and to rank the studies' quality (high, acceptable or low) according to the recommendations of SIGN [26]. The following exclusion criteria were applied: imprecise/heterogenous recording and estimation of stroke incidence, implausible data reporting, methodological differences concerning unclear descriptions of the data source (surveys, diabetes registries or insurance data) or implausible source of diabetes diagnoses. Detailed information can be found in the study protocol.[20]

Results

The systematic search identified 6470 articles, which were assessed by title and abstract. Following initial screening, 230 articles met the criteria for full-text screening, 199 of which were however subsequently excluded, mainly due to missing information for incidence or RRs of stroke or non-population-based study designs. After the critical appraisal, 19 studies which fulfilled our eligibility criteria were included in the analysis (Fig. 1).

The selection procedure is presented in Figure 1.

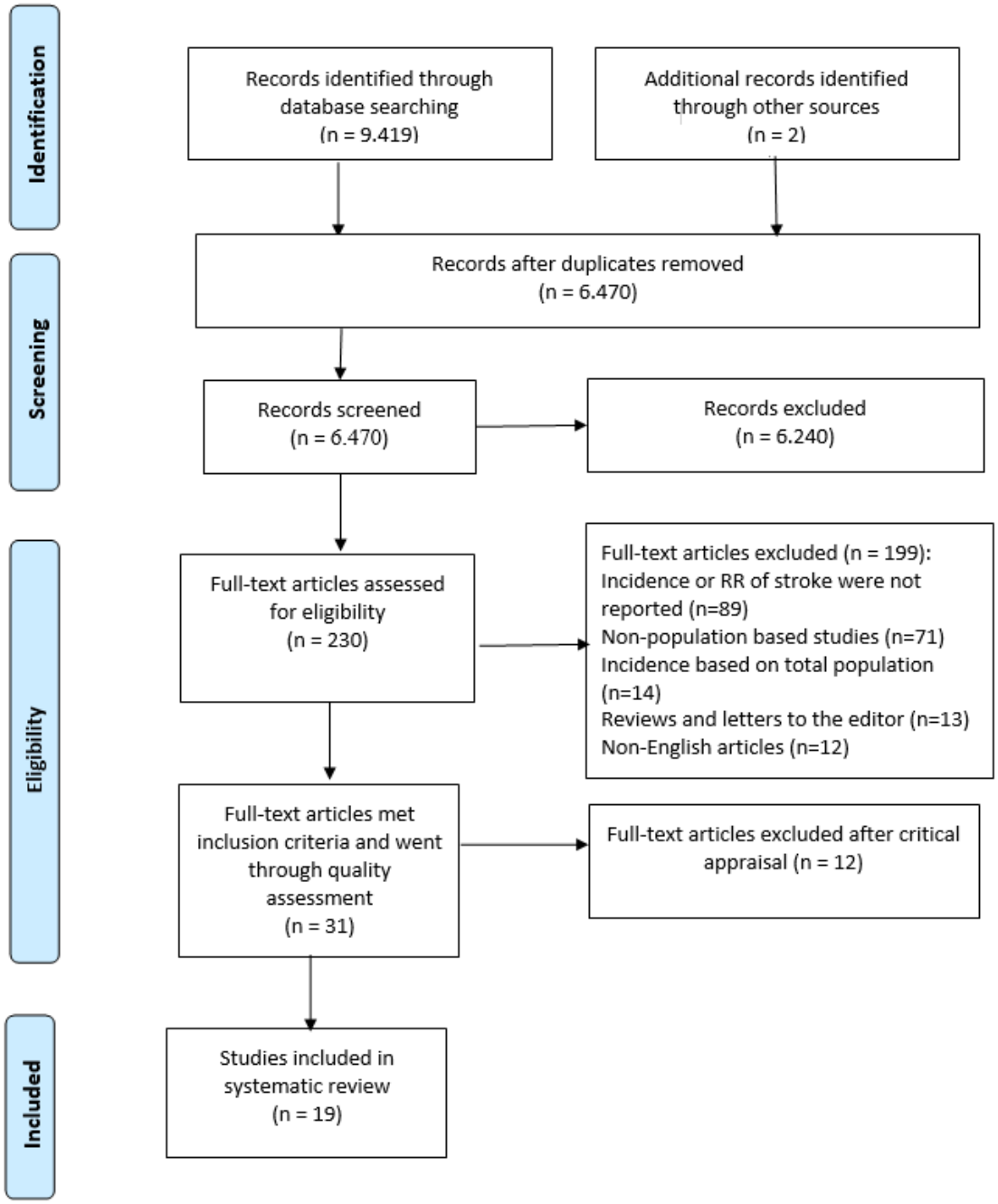


Figure 1: Flowchart of study selection.

Characteristics of studies included in the analysis

Table 1 shows the characteristics of the included population-based studies. Ten of the 19 studies reported data from Europe [5,7,17,28-34], five from the United States (US) [35-39], three from Asia [15,40,41], and one study from Australia [42], No studies reported data from South America and Africa. In total, 16 studies reported data from both sexes, while three studies comprised only a female population [32,36,37].

The majority of the population-based studies included used a prospective cohort study design [15,28,32,34-37,39,42]. Stroke incidence rates were calculated by dividing the number of incidents by the number of person-years of follow-up. Two prospective studies used community-based stroke registers from Germany [29], and Sweden [5]. Five of the included studies used a retrospective cohort study design, comparing the occurrence of first stroke incidences among people with and without diabetes by using health insurance data [17,30,31,40,41]. The included studies used varying data sources to estimate the population with diabetes at risk: six studies used data from national surveys [5,15,29,33,38,39], nine studies used data from national or local diabetes registries or linked data from several diabetes-related data sources [7,32,34-36,40-43], and four studies adopted diabetes prevalence data from other studies [17,28,30,37].

Eight studies did not report specific information on the type of diabetes (type 1 or type 2), instead presenting overall data

about "diabetes mellitus" [5,15,17,30,32,38,39,41]. Seven studies analysed populations with type 2 diabetes [7,28,33,35,36,42,43]. Two studies analysed data separately for type 1 and type 2 diabetes: "The Nurses' Health Study" of a female cohort in the US,37 and the UK Biobank population-based cohort study.34 (see Figure 3) The included studies used different sources to assess the diabetes status of people who had suffered a stroke: eight studies used data based on diagnostic tests or hypoglycemic therapy (treatment for diabetes) [17,28,32,35,36,39,41,42], or a combination of both [29,30,34], four studies used documentation in medical records based on ICD-Codes [33,38,40,43], two studies used self-reported data confirmed by physicians´ diagnoses [15,37], one Scottish study ascertained diabetes status by linkage to a research extract from the Scottish Care Information Diabetes dataset,7 and one study was the Swedish MONICA Stroke Registry study, which was based on the World Health Organization´s (WHO) definition of diabetes [5].

The included studies used different data sources for stroke determination: five studies used data from national surveys [15,32,36,37,39], eight studies were based on hospital or registry data [7,28,30,33-35,38,42], four studies used health insurance data [17,31,40,41] and two studies used data from population-based registries [5,29] All studies used diagnostic criteria for stroke according to ICD-codes 8-10 (the World Health Organization's International Classification of Diseases). The majority of the studies estimated both fatal and non-fatal stroke incidences, with two papers only reporting fatal events [15,36].

Table 1: Characteristics of population-based studies included in the analysis of stroke incidence, fatality and time trends.

Study reference	Study period, population and design	Age range (years)	Gender	Data for diabetic prevalence	Data Source for stroke	Non-fatal/ fatal	Type of stroke	Determination of stroke	Time trend
Folsom et al 1999 USA, [35]	1987/89-1995 Atherosclerosis Risk in Communities (ARIC) Study N=15,792	45-64	Both	Known DM type 2	Hospital data	Non-fatal	IS	Annual telephone contacts; hospital records, hospital discharge	Not reported
Hu et al 2002 USA, [36]	1976-1996 The Nurses' Health Study (NHS) N=117,629	30–55	Women	Known and unknown DM type 2	Survey	Both	All types	Questionnaire confirmed by medical records	Not reported
Mulnier et al 2006 UK, [28]	1992-1999 General Practice Research Database; N=202,733	35-89	Both	Known DM type 2	Hospital data	Both	All types	Medical records, hospital discharge, physiotherapy or rehabilitation, confirmation by computed tomography	Not reported
Janghorbani et al 2007 USA, [37]	1976-2002 The Nurses' Health Study (NHS) N=121,701	30–55	Women	Known DM type 1 and 2	Survey	Both	All types	Questionnaire confirmed by computed tomography, MRI, angiography, surgery, or autopsy	Not reported
Rautio et al 2008 Sweden, [5]	1985-2003 Northern Sweden Stroke Registry, MONICA N= 15,382	35-74	Both	Known DM, n.sp.	Registry	Both	All types [a]	MONICA Registry	+Reported
Icks et al 2011 Germany[b], [17]	2005-2007 Statutory health insurance data, (1.6 million members) N=1,279,530	All	Both	Known DM, n.sp.	Health insurance	Both	All types	Hospitalizations and ambulatory health processes with diagnoses and pharmaceutical prescriptions	Not reported
Khoury et al 2013 USA, [38]	7/1993 - 6/1994, 1999, 2005 5-county Greater Cincinnati/ Northern Kentucky region. N=5,167	≥20	Both	Known DM, n.sp.	Hospital data	Non-fatal	IS	Medical records, hospital emergency, monitoring of all local public health clinics and hospital-based outpatient clinics	Not reported
Schableger et al 2015 Austria, [30]	2008-2012 The Upper Austrian stroke registy (UASR) N=1,319,761	All	Both	Known and unknown DM, n.sp.	Registry and health insurance	Both	All types	The statutory Upper Austrian health insurance	Not reported
Liao et at 2015 Taiwan, [40]	2000-2003 Taiwan's National Health Insurance claims	All	Both	Known DM, n.sp.	Health insurance	Both	All types	Diagnoses for admission and discharge, treatments, medications	Not reported

	N= 24,027 DM cohort N=96,108 non-DM cohort								
Bragg et al 2016 China, [15]	2004–2008 Residents of ten localities across China N=488,760	35–74	Both	Known and unknown DM, n.sp.	Surveillance	Both	All types	Linkage with disease surveillance systems, death certificates	Not reported
Read et al 2017 Scotland, [7]	2004–2013 National Records of Scotland N=69,757	18-89	Both	Known DM type 2	Hospital data and registry	Both	IS and unspecified stroke	National Records of Scotland and national hospitalization register	+Reported
Icks et al 2017 Germany [b], [29]	1998-2014 Community-based stroke register/Erlangen Stroke Project N=105,000	≥ 18	Both	Known and unknown DM, n.sp.	Registry	Both	All types	Computer-linked records systems: hospital admission, discharge, ambulance emergency and general practitioners; death certificates	+Reported
Kiss et al 2018 Hungary, [31]	2010-2013 National Health Insurance Fund (NHIF) N=152,678 DM typ 2 cohort N=305,356 matched controls cohort	All	Both	Known DM type 2	Health insurance	Both	All types*	Outpatient records, all-cause mortality data	Not reported
Price et al 2018 UK, [32]	1996-2001 UK Million Women Study N=712,433	All	Women	Known and unknown DM, n.sp.	Survey	Both	IS, ICH, SCH	Linkage to National Health Service database: deaths and hospital admissions	Not reported
Malla et al 2019 USA, [39]	2003–2007 to 2017 The Reasons for Geographic and Racial Differences in Stroke (REGARDS) N=30,183	≥ 45	Both	Known DM, n.sp.	Survey	Both	All types	Computer-assisted telephone interview. Semi-annual follow-up from medical records	Not reported
Davis et al 2020 Australia, [42]	1993-1996, 2008-2011, Community-based Fremantle Diabetes Study N=13,995	All	Both	Known DM type 2	Hospital data	Both	All types	The hospital morbidity data	Not reported
Peters et al 2020 UK (England, Scotland, and Wales), [34]	2006-2018 UK Biobank prospective, population-based cohort Study N >500,000	40-69	Both	Known DM type 1 and 2	Hospital data, death register and Biobank	Both	All types	Hospital admissions data by ICD- codes and the national death register; UK Biobank	Not reported
Kim et al 2021 South Korea, [41]	2004-2015, National Health Insurance Service, population-based Cohort N= 514, 866	40 -79	Both	Known DM, n.sp.	Health insurance	Both	SCH	Health insurance claims data for all hospital visits (include diagnostic code, procedure performed, prescriptions issued)	Not reported
López-de-Andrés et al 2021 Spain, [33]	2016-2018, The Spanish National Hospital Discharge Database, 95% of all hospital in Spain	≥35	Both	Known DM type 2	Hospital data	Both	IS	Hospital discharges	Not reported

[a]Subarachnoidal hemorrhages were excluded; b Data was extracted from people who were not involved in the study by Icks et al.
IS, ischaemic stroke; ICH, intracerebral hemorrhage; SCH, subarachnoid hemorrhage; n. sp, no specific information collected on diabetes type.

Incidence and relative risks of stroke

The results are presented in Table 2.

Total stroke (all types of strokes)

Thirteen studies estimated incidence rates of all types of stroke (IS, ICH, SCH) for both non-fatal and fatal stroke [5,17,28-31,34,37,40,42] The IRs ranged from 238 (155-321) in Germany in 2014 [29] to 1191 (1,141–1,243) in the UK in the 1990s (data from 1992-1999) [28] per 100,000 PY in the population with diabetes and from 208 (200–219) [17] to 555 (540–570) in the population without diabetes [28]. The RRs in the same studies ranged from 1.0 (0.7-1.5) to 2.19 (2.1–2.3). With regard to gender differences, some studies described slightly higher RRs among women [28,30,31,40] However, a German study (data from 1998-2014) by Icks et al. found the RR to be somewhat higher among men in the first years of the study period, while similar values were seen in later years for both sexes [29].

In general, there was no consistent gender pattern. Regarding age differences, a more pronounced effect was observed among younger groups in the US by Malla et al., where the HR for total stroke was higher among the age group <65 years than among older people aged ≥65 years (Table 2) [39]. In the study by Mulnier, the risk of stroke associated with diabetes decreased with age and was highest among young people (age 35–54 years: HR 5.64 (3.91–8.13) vs. age 75–84 years: 1.90 (1.75–2.06) (data not shown), [28] Similarly, the studies from Scotland, [7] and Austria, [30] found a more pronounced risk of stroke incidence among younger age groups than among older people (data not shown).

Table 2: Incidence rates, relative risks and time trends of stroke among the populations with and without diabetes (+).

Incidence rates (95% CI) per 100,000 person years					RR/HR/IRR (95% CI)		Time trend	
Study	Total population		Stratified by sex/ethnic origin		Total population	Stratified by sex/ethnic	DM	Non-DM
	DM	non-DM	DM	non-DM				
Total stroke both *non*-fatal and fatal								
Mulnier 1992-1999 UK, [28]	1191 (1141-1243) †	555 (540-570) †	m 1082 (1020-1150) † w 1316 (1200-1400) †	m 526 (505-547) † w 587 (565-620) †	HR 2.19 (2.1–2.3)	HR m 2.08 (1.9-2.2) w 2.32 (2.2-2.5)	-	-
Janghorbani 1976-2002 women cohort USA, [37]	-	-	w Type 1: 475 Type 2: 240	w 92	-	RR Type 1: 4.7 (3.3-6.6) Type 2: 1.8 (1.7-2.0)	-	-
Rautio 1985-2003 Sweden [a], [5]	-	-	-	-	-	-	IR m: n.s. decreased per y 0.1% (0.9-1.0, p<0.912) w: sign. decreased per y 1.5% (0.3-2.7, p=0.012)	IR m: sign. decreased per y 0.8% (0.3-1.3, p<0.001) w: remain stable 0.0 (0.6 -0.6, p<0.981)
Peters 2006-2018 UK, [34]	-	-	Type 1 w 378 (170–571) † m 331 (151-511) † Type 2 w 130 (100–151) † m 191(161–220) †	w 88 (84–93) † m 125 (112–130) †	-	-	-	-
Davis 1993-1996/ 2008-2011, Australia, [42]	1993-1996: 930 † 2008-2011: 509†	1993-1996: 411 † 2008-2011: 451†			HR 1993-1996: 2.84 (2.07-3.91) 2008-2011: 1.13 (0.78-1.63)		-	-
Icks (2011) 2005-2007, Germany [b], [17]	402 (376–479)	208 (200-219)	m 476 (438-514) w 342 (305-378)	m 255 (243-266) w 173 (163-182)	RR 1.9 (1.8-2.1)	RR m 1.9 (1.7–2.0) w 2.0 (1.8–2.2)	-	-

Icks (2017) 1998-2014, Germany [b], [29]	1998: 401 (279-523) 2014: 238 (155-321)	1998: 212 (174-250) 2014: 235 (199-271)	m 1998: 480 (282-679) 2014: 263 (155-370) w 1998: 336 (180-493) 2014: 219 (93-345)	m 1998: 196 (136-256) 2014: 262 (203-320) w 1998: 218 (170-267) 2014: 211 (167-255)	RR 1998: 1.88 (1.3-2.6) 2014: 1.0 (0.7-1.5)	RR m 1998: 2.4 (1.4-4.1) 2014: 1.004 (0.63-1.5) w 1998: 1.5 (0.9-2.6) 2014: 1.03 (0.56-1.91)	RR 0.98 (0.97-0.99) sign.decrease per year by 0.5%	RR 1.003 (0.993-1.013) remained constant no consistent change
Schableger 2008-2012 Austria, [30]	591 (562-621)	329 (323-334)	m 572 (530-613) w 600 (559-642)	m 319 (311-327) w 343 (335-351)	-	-	-	-
Liao 2000-2003 Taiwan, [40]	1010†	450†	m 1090† w 941†	m 528† w 375†	HR 1.75 (1.6-1.8)	HR m 1.60 (1.4-1.7) w 1.93 (1.7-2.1)	-	-
Kiss 2010-2013 Hungary [a], [31]	-	-	-	-	HR 1.40 (1.3-1.4)	HR m 1.33 (1.2-1.4) w 1.47 (1.4-1.5)	-	-
Malla 2019 USA, [39]	-	-	-	-	-	HR <65 y: WP w 3.7 (2.1-6.5) AA w 1.8 (1.2-2.9) WP m 2.0 (1.2-3.2) AA m 1.27 (0.7-2.1) ≥65: WP w 1.79 (1.2-2.5) AA w 1.05 (0.7-1.4) WP m 0.86 (0.6-1.2) AA m 1.68 (1.1-2.5)		
Total stroke non-fatal								
Hu2002 USA, [36]	-	-	-	-	-	RR w 5.28 (4.28-6.52)	-	-
Bragg 2016 China, [15]	981.7	553.5	-	-	HR 1.39 (1.3-1.4)	-	-	-
Total stroke fatal								
Hu 2002 [36]	-	-	-	-	-	RR w 7.42 (5.91-9.32)	-	-
Bragg [15]	129.1	56.9	-	-	HR 1.66 (1.4-1.9)			
Ischemic stroke both non-fatal and fatal								
Janghorbani 1976-2002 USA. [37]	-	-	w Type 1: 20 Type 2: 373	w 42	-	RR Type 1: 6.3 (4.0-9.8) Type 2: 2.3 (2.0-2.6)	-	-
Read 2004-2013 Scotland, [7]	-	-	-	-	IRR 1.15 (1.09-1.27)	IRR m 2004: 1.28 (1.2-1.3) 2013: 1.21 (1.1-1.3) w 2004: 1.43 (1.3-1.5) 2013: 1.42 (1.3-1.5)	IRR n.s decrease per y by 1.26% (0.66-1.87)	IRR 0.99 (0.98- 1.01) remained constant
Icks 2017 Germany, [29]	1998: 258 (179-336) 2014: 209 (130-288)	1998: 190 (154-226) 2014: 207 (173-241)	m 1998: 309 (163-455) 2014: 231 (131-332) w 1998: 213 (128-298) 2014: 194 (71-318)	m 1998: 181 (123-240) 2014: 228 (173-282) w 1998: 192 (146-238) 2014: 186 (144-228)	RR 1998: 1.3 (0.94-1.9) 2014: 1.0 (0.7-1.5)	RR m 1998: 1.7 (0.9-3.0) 2014: 1.01 (0.62-1.66) w 1998: 1.1 (0.7-1.7) 2014: 1.0 (0.53-2.04)	RR: n.s decrease per y by 1%, 0.99 (0.97-1.00) no consistent change	RR: 1.002 (0.99-1.01) remained constant
Price 1996-2001 UK, [32]	-	-	-	-	-	RR w 2.01 (1.84-2.20)	-	-
Peters 2006-2018 UK, [34]	-	-	-	-	-	HR Type 1 w 6.54 (3.79-11.27) m 3.31 (1.96-5.60) Type 2 w 1.88 (1.56-2.27) m 1.51 (1.32-1.71)	-	-
López-de-Andrés 2016-2018 Spain, [33]	111.61	27.93	m 124.68 w 98.33	m 30.83 w 25.29	IRR 2.02 (1.99-2.04)	IRR m 2.19 (2.16-2.22) w 1.77 (1.75–1.80)	-	-
Ischemic stroke non-fatal								

Folsom 1999 USA, [35]	538†	151†	AA 942† WP 367†	AA 226† WP 116†	RR 3.70 (2.7-5.1)	-	-	-
Khoury 2013 USA, [38]	-	-	AA: 1993/94: 1.33 (1.03-1.62) 2005: 617 (496-737) WP: 1993/94: 549 (484-614) 2005: 504 (443-565)	AA: 1993/94: 241 (208-275) 2005:216 (185-246) WP: 1993/94: 169 (159-246) 2005: 145 (136-154)	-	IRR AA 1993/94: 5.6 (4.2-7.1) 2005: 3.2 (2.4-3.9) WP: 1993/94: 3.8 (3.2-4.3) 2005: 3.8 (3.3-4.3)	-	-
Bragg 2016 China, [15]	869.5	463.6	-	-	HR 1.47 (1.4-1.6)	-	-	-
Ischemic stroke fatal								
Bragg 2016 China, [15]	19.3	8.6	-	-	HR 1.85 (1.3-2.6)	-	-	-
Hemorrhagic stroke both non-fatal and fatal								
Janghorbani 1976-2002 USA, [37]	-	-	-	-	-	RR Typ 1: 3.8 (1.2-11.8) Typ 2: 1.0 (0.7-1.4)	-	-
Price 1996-2001 UK, [32]	-	-	-	-	-	RR ICH: 1.31 (1.04-1.65) SCH: 0.43 (0.26-0.69)	-	-
Kim 2004-2015 South Korea, [41]	17.1 (13.5-21.4)	21.7 (20.3-23.1)	-	-	HR 0.68 (0.53-0.86)	-	-	-
Hemorrhagic stroke non-fatal								
Bragg [15]	69.1	42.6	-	-	HR 0.8 (0.64-1.0)	-	-	-
Hemorrhagic stroke fatal								
Bragg [15]	96.8	42.6	-	-	HR 1.6 (1.3-1.9)	-	-	-

Abbreviations: DM, diabetes; RR, relative risk; HR, hazard ratio; IRR, incidence rate ratio; ICH, intracerebral hemorrhage; SCH, subarachnoid hemorrhage; m, men; w, women; WP, white persons; AA, African-American.
Notes: (+) age-standardized or age-adjusted incidence rates were considered; † self-calculated; (-) not reported; [a] subarachnoidal hemorrhages were excluded; [b] data was extracted from people who were not involved in the study by Icks et al.

Ischemic stroke

Six population-based studies were identified which assessed IS separately among populations with and without diabetes [7,29,32-34,37] Only two of those studies reported incidence rates of IS per 100,000 PY [17,33,37], ranging from 111.6 in Spain (2018) [33] to 258 in Germany (1998) [29] in the population with diabetes, and 27.9 (Spain) to 186 (Germany) for the population without diabetes. Two of the six studies compared IRs of ischaemic stroke among men and women [29,33]. The IR per 100,000 PY decreased in the population with diabetes from 258.1 (179-336) in 1998 to 111.6 in 2018. In contrast, the IR remained relatively constant among the population without diabetes in Germany: 190.4 (154-226) in 1998 and 207.6 (173-241) in 2014.

Higher IRs were observed among men with diabetes, whereas the results among people without diabetes were comparable for both sexes (Table 2) [29,33]. In the UK study [34], type 1 diabetes was associated with a substantially higher risk of ischemic stroke in both women and men: the multiple-adjusted HR of IS was 6.54 (3.79–11.27) in women and 3.31 (1.96–5.60) in men. In the study by Read, diabetes was associated with a 45% and 26% increased risk of ischemic stroke among women and men respectively. In the German study, the RR of IS was not significantly different, ranging from 1.3 (0.94–1.93) in 2001 to 1.0 (0.7–1.5) in 2014. Two female cohort studies from the US and the UK showed that diabetes was strongly associated with IS, with RRs of IS being twice as high among women with diabetes (Table 2) [32,37].

Hemorrhagic stroke

Four studies estimated the IR for hemorrhagic stroke. [15,32,37,41] In a study from the US, type 1 diabetes was significantly associated with the risk of hemorrhagic stroke among women (RR=3.8 (1.2–11.8)), whereas type 2 diabetes was not (RR=1.0 (0.7–1.4)) [37]. While the RR of intracerebral hemorrhage was increased (RR=1.31) in women with DM in the UK (Million Women Study), the risk of SCH was approximately 56 % (RR=0.43.9 (0.26–0.69)) lower in women with diabetes compared to women without diabetes. Results were broadly similar in the Korean study from 2021 where type 2 diabetes was significantly associated with decreased risk of subarachnoid haemorrhage (adjusted HR=0.68 (0.53-0.86)) [41]. No studies reported the effect of diabetes on hemorrhagic stroke among men only.

Fatal vs. non-fatal stroke

A number of studies from the USA and China reported fatal and non-fatal stroke incidences separately (Figure 2 A, B) [15,35,36,38].

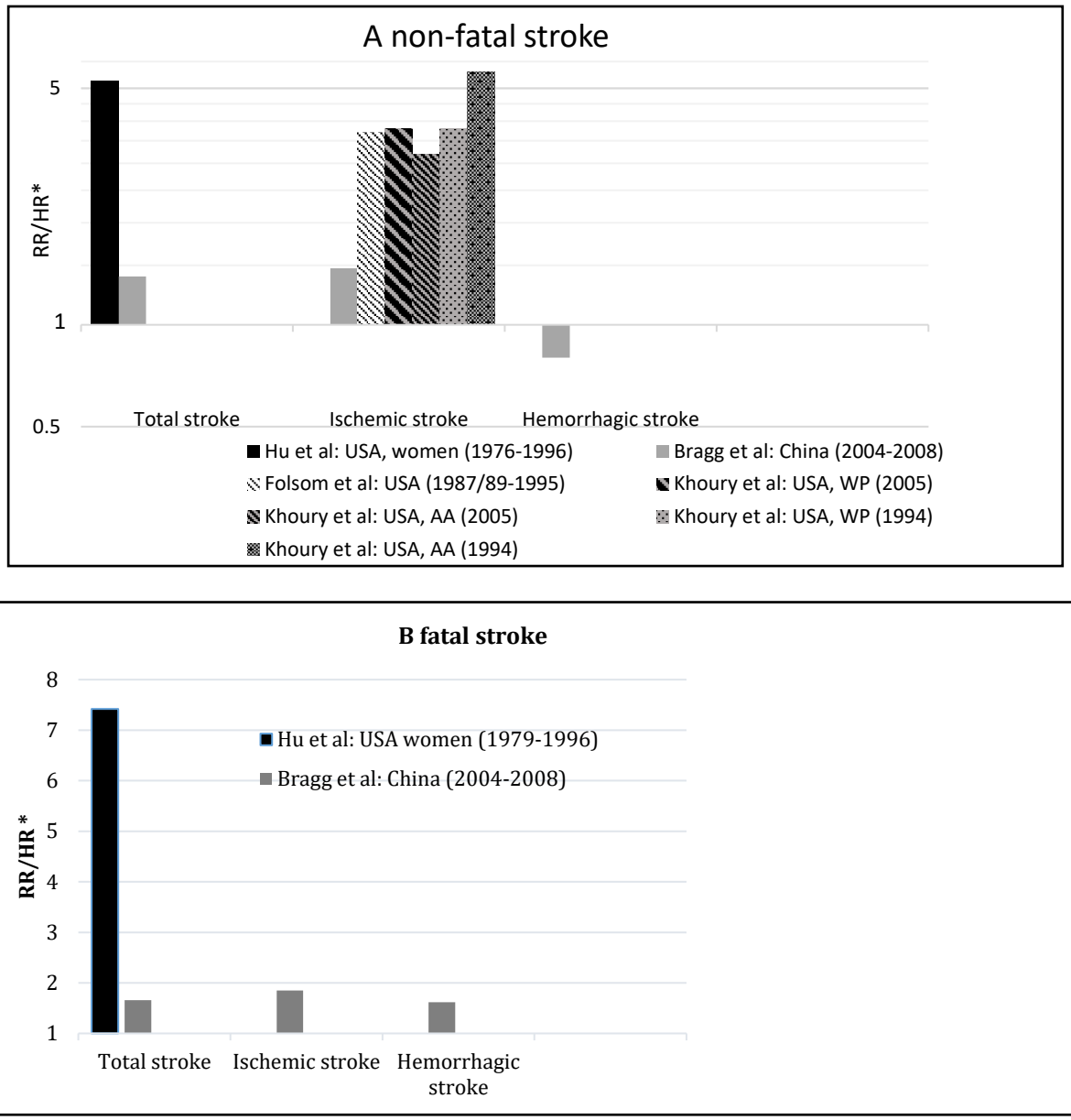


Figure 2 (A, B): Fatal vs. non-fatal stroke. RR/HR* population with diabetes compared to population without diabetes; WP, White persons; AA, African-American (Figure 3A).

In a cohort study (data from 1976-1996 "The Nurses' Health Study"), Hu et al. showed that the RRs for non-fatal and fatal stroke were significantly higher among women with diabetes aged 30-55 years (5.28 and 7.42 respectively) compared to other studies [36]. A study from China found the risk of non-fatal hemorrhagic stroke to be approximately 20% (RR: 0.8 (0.64-1.0)) lower in the population with diabetes compare to people without diabetes [15].

Khoury et al. compared ethnic differences for non-fatal IS (Figure 2a) and found the risk of IS among African-Americans to have decreased significantly from 5.6 in 1994 to 3.2 in 2005, while the risk among White people remained the same at 3.8 in 1994 and in 2005 [38].

Time trends of incidence rates and relative risks

Three studies described the time trend among the population with and without diabetes with contradictory results [5,7,29]. The results are presented in Table 2. The study by Icks et al. found a significant annual decrease (1.5%) in the incidence of all stroke types (fatal and non-fatal) among people with diabetes, with similar results among men and women. In contrast, incidence remained constant among individuals without diabetes,29 (Table 2) in both sexes. RRs in this study decreased by 2% per year (RR per calendar year 0.979; 0.960±0.997), with similar results for both sexes. A slight annual decrease in the IR of ischemic stroke of 1% was reported for the population with diabetes (RR per calendar year 0.99; 0.97-1.00), with comparable results among men and women. The IR remained nearly constant with similar results for both sexes among the population without diabetes. Rautio, [5] analyzed all stroke types except subarachnoidal haemorrhage in Sweden from 1985 to 2003 and found declining IRs among women with diabetes (1.5% per annum) and men without diabetes (0.8% per annum), but not among men with diabetes (n.s. 0.1% (0.9-1.0, annual change). IRs among women without diabetes also remained stable (Table 2) [5]. In Scotland

between 2004 and 2013 incidence rates of ischemic stroke declined by 1.26% (0.66-1.87) annually among people with diabetes and in people without diabetes in Scotland between 2004 and 2013 (diabetes/year interaction: rate ratio 0.99 (0.98-1.01)) [7].

Discussion

The data from the 19 population-based studies included in this systematic review show the incidence of all stroke types (except hemorrhagic stroke) to be greater among individuals with diabetes than among those without [29,41] However, our analysis observed variations in the incidence of stroke and RR of stroke between the populations with and without diabetes. This variation may be due to the large heterogeneity of the included studies. Most studies reported data on all types of non-fatal and fatal stroke combined without differentiating between ischemic or hemorrhagic stroke and fatality or non-fatality. We identified only few studies of time trends which compared populations with und without diabetes meeting our eligibility criteria. These studies indicated relatively stable IRs of stroke over time among people without diabetes and decreasing rates among people with diabetes.

Ischemic vs. hemorrhagic stroke

Six population-based studies included in this review reported the IR and RRs/HRs for ischemic stroke [7,29,32-34,37] and these studies for hemorrhagic stroke [32,37,41]. Interestingly, the risk of subarachnoid hemorrhage was approximately 30-50% lower among people with diabetes compared to people without diabetes. Our findings were consistent with the results of a recent systematic review and meta-analysis of risk factors for ischemic and hemorrhagic stroke [44]. Luitse et al. reported that admission hyperglycemia is associated with poor functional outcome, possibly due to aggravated ischemic damage as a result of disturbed recanalisation and increasing reperfusion injury [45]. A further study indicated that hyperglycemia among patients with hemorrhagic stroke is an independent risk factor for poor clinical outcomes and may affect the increase in size of hematom [46]. As the studies report, several mechanisms may play a role in these relationships. For example, poorly controlled hyperglycemia reduces cerebral blood flow and oxygenation of tissues and increases intracranial pressure, cerebral edema and neuronal death [47] As reported by Snarska et al., [48] these mechanisms, which are more severe among patients with diabetes and hemorrhagic stroke, may increase mortality.

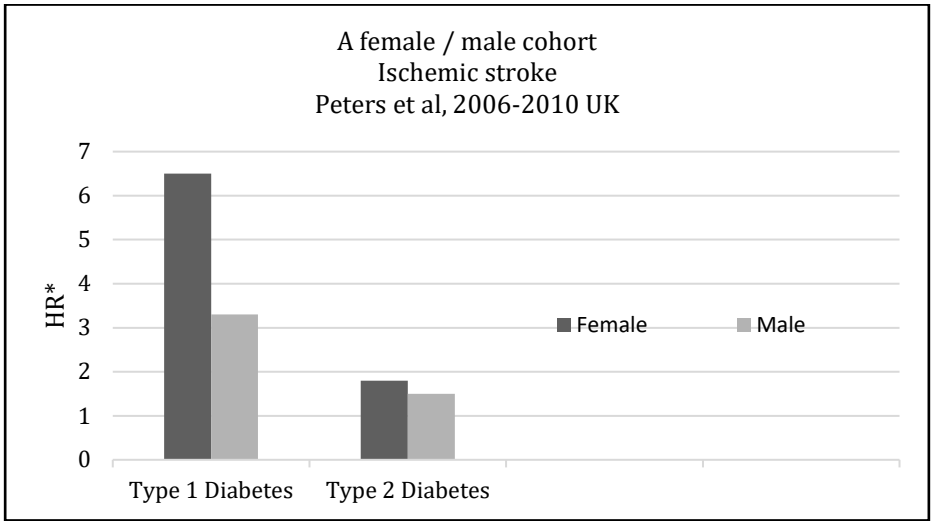
Time trend

Our review only found limited data regarding time trends: just three of the 19 studies of time trends in the the populations with and without diabetes met our eligibility criteria. Two studies identified decreasing time trends in people with diabetes and stroke (all types) than without diabetes [5,29]. Decreasing time trends were also found for ischaemic stroke in persons with diabetes, while time trends remained constant in populations without diabetes [7,29].
Our study confirms the findings of other reports. For example, in the US, the RR of stroke associated with diabetes declined from 2.5 in 2000 to 1.5 in 2010 [49] In contrast, the incidence trends of all stroke types and of just ischemic stroke remained constant among individuals without diabetes in Germany and in Scotland [7,29]. In Sweden, IRs of stroke were found to decline by 0.8% per year among men without diabetes, whereas the IR remained constant among women without diabetes [5]. These positive results among the population with diabetes may reflect improved management of diabetes, hypertension and dyslipidemia, as well as population-wide improvements in diets and reduced smoking prevalence [7] Secondary prevention measures for patients with diabetes and established cardio-vascular diseases (CVD) should therefore be intensified, with interventions focusing on traditional cardiovascular risk factors [5].

The results presented regarding time trends among people without diabetes are in line with international studies, which identified stable incidences among the general population [50-52]. A systematic review by Feigin et al. which included population-based studies from 28 countries from 1970 to 2008 found a 42% decrease in stroke incidence, especially ischemic stroke, in high-income countries [53]. Similarly, a review using data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD Study) reported a significantly declining trend in the age-standardized incidence of stroke from 1990–2013 in high-income countries.[54] In contrast, studies from low- and middle-income countries mainly reported trends of increasing stroke incidence [55].

Diabetes type 1 and type 2

Two cohort studies from the US [37], and UK [34], reported stroke data separately for type 1 und type 2 diabetes (Figure 3 A, B).



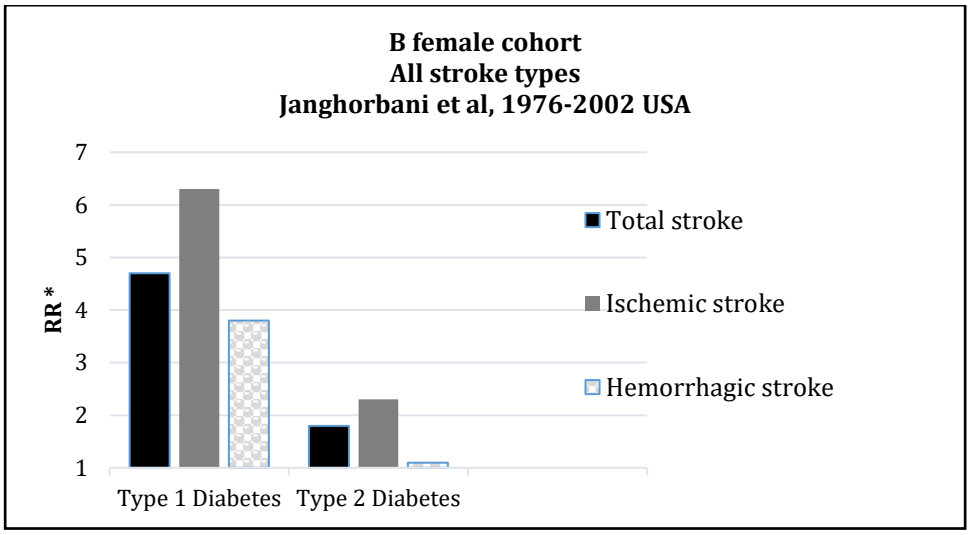


Figure 3 (A, B): Risk of Stroke Per Diabetes Type and Sex. Hr/Rr*: Population with Diabetes Compared to Population Without Diabetes.

Both studies found type 1 diabetes to markedly increase the risk of all stroke subtypes among women. Even after controlling for age, body mass index (BMI), physical activity, menopausal status, estrogen use, smoking, hypertension, high cholesterol, ischemic heart disease, aspirin use, and alcohol consumption, the risk of ischemic stroke was 6.3 times higher in women with type 1 diabetes compared to women without diabetes (Figure 3b).

The risk of hemorrhagic stroke was almost four times higher, and of total stroke 4.7 times higher in the US female cohort (Figure 3b) [37]. However, as the authors noted, the results were based on few cases and should therefore be interpreted with caution. Similarly, a UK study including both sexes also found that for type 1 and type 2 diabetes the HRs for ischemic stroke were higher among women than men (Figure 3a) [34]. Type 2 diabetes was not found to pose a significant risk for hemorrhagic stroke (RR: 1.1 (95% CI 0.7–1.4)), but the RR of ischemic stroke was increased twofold (2.3 (2.0 –2.6)) [37]. Data on type 2 diabetes relating to the risk of intracerebral hemorrhage were limited and conflicting [56].

Most studies reported type 2 diabetes to be an important risk factor for ischemic stroke but not to increase the incidence of hemorrhagic stroke [9,57-59]. This finding may partly reflect the longer duration of type 1 diabetes than type 2 diabetes. This is supported by the fact that the magnitude of the positive relation between type 2 diabetes and the risk of myocardial infarction, heart failure, and ischemic stroke increased with longer duration of type 2 diabetes [58]. Another possible explanation for of the differences regarding diabetes types is that treatments may differ for patients with type 1 (insulin therapy) and type 2 diabetes (usually diet and exercise alone or combined with diabetes medications). Hägg [59]. also reported partial differences between the risk factor profiles of type 1 diabetes for ischemic stroke and hemorrhagic stroke. Longer duration of diabetes, presence of diabetic nephropathy, poor glycemic control, more severe diabetic retinopathy, history of smoking, and insulin resistance all independently increased the risk of ischemic stroke. The risk factor profile for hemorrhagic stroke included presence of diabetic nephropathy and diabetic retinopathy, higher systolic blood pressure, and lower BMI. Due to the heterogeneity and limitations of the results, future large

studies of the association between types of diabetes and the risk of different stroke types are necessary to better understand their relationship.

Gender and age difference

The findings of the included studies were inconsistent. Some studies found higher IRs among men [17,29,33,34,40,48], than women in both the population with and without diabetes. However, most studies reported higher RRs in women, ranging from 1.47 [31], to 2.3 [28] for all stroke types and from 1.04 [29], to 1.88 [34], for ischemic stroke. This association between the risk of stroke and female gender was described in earlier publications [9,60,61]. A large meta-analysis reported a 27% higher RR of stroke due to diabetes among women compared to men [9].

Our review only indicated beneficial time trends among women. The first stroke did not change among women without diabetes [5]. In contrast, the study by Icks et al. (2017) [29] did not identify any gender differences regarding time trends. We identified a number of studies which found the risk of stroke to be higher among the young population with diabetes [7,15,28,29,37,38]. In the Mulnier study from the 1990s, the increased risk associated with diabetes decreased with age and was highest among young women (aged 35–54 years: HR=8.18 (4.31–15.51)) [28]. Data from the Nurses' Health Study from the US covering the time period 1976-2002 showed similar results, with a higher incidence of stroke attributable to younger age at onset of diabetes [37]. The German study by Icks et al. also found the RR for stroke to decrease with increasing age: RR diabetes vs. no diabetes < 50 years: 3.43; 80+ years: 1.1 [29]. An Austrian study found diabetes to have the most severe influence on the incidence of stroke among persons in the 0-44 age group [30], with the risk of stroke being 5.44 (men: 5.55, women: 5.26) times higher among people with diabetes than without. While the risk of stroke in people with diabetes in the age group 45-54 years was indeed considerably lower, it was still more than twice as high than in people without diabetes in the same age group. In a recent study from Scotland, the risk of ischemic stroke was most pronounced in the age group <60 years [7].

Our findings confirm those of past studies which found the association between diabetes and stroke to be more pronounced among young and middle-aged adults than in older adults. In the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), the risk of stroke associated with diabetes was greater among adults aged <65 than those aged ≥65 years. Similarly, the recently updated Framingham Heart Study (Revised Framingham Stroke Risk Profile to Reflect Temporal Trends) reported stronger association at a younger age [62] One possible explanation for the age differences in diabetes-related relative risk of stroke is the proportional increase in numbers of risk factors with increasing age among people without diabetes [16]. Moreover, Kiss [43], found age-related differences in statin medication adherence, with the younger cohort presenting significantly lower adherence than older cohorts. It was found that those people who did not adhere to statin intake were significantly younger, more likely to be female and had a significantly shorter duration of diabetes [63].

Ethnic differences

There is little information regarding the impact of ethnic differences on the association of diabetes with stroke. Only three studies in our review, all from the US, reported ethnic differences [35,38,39]. The results are contradictory (see Table 2 and Figure 2). The ARIC (Atherosclerosis Risk in Communities, 1987–1995) Study by Folsom et al. did not, however, identify any ethnic differences regarding the diabetes-stroke association [35], although an updated analysis with additional follow-ups found the diabetes-stroke association to be stronger among black adults than among white adults [64].

Strengths and limitations

This systematic review incorporated a number of studies published over the past 30 years, giving a current overview of incidence and risk of stroke among the populations with and without diabetes. One major strength of our review is the selection of included studies using a systematic search approach with clearly determined search strategies. We only included those studies reporting stroke incidences among the population at risk, i.e. the population with diabetes. This method is advantageous because results are not influenced by changes in the prevalence of diabetes. Moreover, we analysed stroke incidences for separate groups considering the definitions of different stroke types, including fatal and non-fatal stroke. This approach allowed studies to be compared despite a high degree of heterogeneity.

Nevertheless, our review has some limitations. Although seven databases were searched, relevant studies might be missing due to publication bias. Furthermore, studies that were published in languages other than English were excluded. Most studies reporting on stroke incidence and time trends were conducted in high-income countries, such as the US or European countries, and thus do not represent a worldwide perspective.

This comprehensive systematic review demonstrates the considerable variation of stroke incidence among the population with diabetes and without diabetes, probably in part due to the heterogeneous design of the identified studies. Only few studies investigated time trends.

Conclusion

We found decreasing time trends in people with diabetes and stable incidence rates of stroke over time in people without diabetes. Risk of subarachnoid hemorrhage was approximately 30-50% lower among people with diabetes compared to people without diabetes. We identified a number of studies which found the risk of stroke to be higher among the young population with diabetes. Future studies analysing the incidence and RRs of stroke among the population with diabetes could use a more comparable study design such as prospective studies with detailed information regarding the clinical definition, cause and recording of stroke as well as the better defined population at risk.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests
Non-financial competing interests in this work.

Authors' contributions
All authors were involved in the design of the review. Tatjana Kvitkina, Maria Narres and Heiner Claessen undertook analysis of the data and drafted the manuscript. Maria-Inti Metzendorf performed literature search. Andrea Icks and Bend Richter carefully revised the manuscript. All authors reviewed the manuscript, contributed to its revision, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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