Temporal Trends in Sex Differences With Regard to Stroke Incidence

The Dijon Stroke Registry (1987–2012)

Marie Giroud, MD; Benoit Delpont, MD; Benoit Daubail, MD; Christelle Blanc, MD; Jérôme Durier, MSc; Maurice Giroud, MD; Yannick Béjot, MD, PhD

Background and Purpose—We evaluated temporal trends in stroke incidence between men and women to determine whether changes in the distribution of vascular risk factors have influenced sex differences in stroke epidemiology.

Methods—Patients with first-ever stroke including ischemic stroke, spontaneous intracerebral hemorrhage, subarachnoid hemorrhage, and undetermined stroke between 1987 and 2012 were identified through the population-based registry of Dijon, France. Incidence rates were calculated for age groups, sex, and stroke subtypes. Sex differences and temporal trends (according to 5-year time periods) were evaluated by calculating incidence rate ratios (IRRs) with Poisson regression.

Results—Four thousand six hundred and fourteen patients with a first-ever stroke (53.1% women) were recorded. Incidence was lower in women than in men (112 versus 166 per 100 000/y; IRR, 0.68; $P<0.001$), especially in age group 45 to 84 years, and for both ischemic stroke and intracerebral hemorrhage. From 1987 to 2012, the lower incidence of overall stroke in women was stable (IRR ranging between 0.63 and 0.72 according to study periods). When considering stroke subtype, a slight increase in the incidence of ischemic stroke was observed in both men (IRR, 1.011; 95% confidence interval, 1.005–1.016; $P=0.001$) and women (IRR, 1.013; 95% confidence interval, 1.007–1.018; $P=0.001$). The sex gap in incidence remained unchanged in ischemic stroke and intracerebral hemorrhage. Conversely, the lower subarachnoid hemorrhage incidence in women vanished with time because of an increasing incidence.

Conclusions—The sex gap in stroke incidence did not change with time except for subarachnoid hemorrhage. Despite lower rates, more women than men experience an incident stroke each year because of a longer life expectancy. **(*Stroke*. 2017;48:846-849. DOI: 10.1161/STROKEAHA.116.015913.)**

Key Words: epidemiology ■ incidence ■ income ■ registry ■ stroke

Sex differences in the incidence of stroke have been well established. A meta-analysis of epidemiological studies reported a 33% greater stroke incidence in men than in women.[1] Nevertheless, most of the studies included in this meta-analysis were conducted at the end of the 20th century, and data about temporal trends in sex differences regarding stroke incidence are scarce. Based on the recent estimates of the GBD study (Global Burden of Disease), the excess in stroke incidence in men compared with women was 30% in 1990 and 34% in 2013.[2] Of note, both high-income and low-to-middle income countries were included in the analyses.

Whether changes in the distribution of vascular risk factors in recent decades in the populations of developed countries has had an impact on the sex gap in stroke incidence remains to be determined. Therefore, we aimed to assess temporal trends in stroke incidence rate ratios (IRRs) between men and women from 1987 and 2012, by taking into consideration stroke subtypes.

Methods

Study Population and Case-Ascertainment Procedures

The Dijon Stroke Registry, which was established in the 1980s, is an on-going population-based study conducted among the population of the city of Dijon, France (currently 151 543 inhabitants).[3] It complies with the defined criteria for conducting ideal incidence stroke studies.[4] Methodology of case ascertainment and adjudication has been extensively described elsewhere.[3] Briefly, multiple overlapping sources of information based on hot and cold pursuit procedures are used to identify all cases of stroke in this geographically defined area, whatever their management (as inpatients or outpatients).[3] Records of all suspected cases are reviewed by neurologists trained in stroke ascertainment. Stroke adjudication is based on meetings of study investigators.

Stroke was defined according to World Health Organization diagnostic criteria.[5] Stroke subtypes were classified as ischemic stroke (IS), spontaneous intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), according to clinical signs confirmed by brain imaging and complementary examinations. Stroke was classified as

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From the Dijon Stroke Registry, EA4184, University Hospital and Medical School of Dijon, University of Burgundy, France (Marie Giroud, B. Delpont, B. Daubail, C.B., J.D., Maurice Giroud, Y.B.); and Department of Neurology, CH William Morey, Chalon-sur-Saône, France (Marie Giroud).

Correspondence to Yannick Béjot, MD, PhD, Dijon Stroke Registry, Department of Neurology, University Hospital of Dijon, Hôpital François Mitterand, 14 rue Paul Gaffarel, BP 77908, 21079 Dijon cedex, France. E-mail ybejot@yahoo.fr

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undetermined if no imaging was performed. For the present study, patients with a first-ever stroke who were registered between January 1, 1987, and December 31, 2012, were included.

Statistical Analysis

Crude incidence rates were calculated for age groups, sex, and stroke subtypes. Denominators concerning the population of Dijon according to 1-year age groups and sex were based on census data for 1990, 1999, and 2007 provided by the National Institute of Statistics. The population was estimated from these censuses by linear interpolation. Age-standardized rates were evaluated by the direct method with the European standard population as standard.[6] Confidence intervals (CIs) for the incidence rate estimates were calculated using the Poisson distribution. To assess sex differences in stroke incidence, IRRs were calculated using a Poisson regression. For the evaluation of temporal changes in incidence, the results were presented according to 5 study periods: 1987 to 1991, 1992 to 1996, 1997 to 2001, 2002 to 2006, 2007 to 2012, and IRRs were calculated using a Poisson regression and adjusted for age groups. *P* values <0.05 were considered statistically significant. Statistical analysis was performed with STATA@13 software (StataCorp LP, College Station, TX).

Ethics

The Dijon Stroke Registry was approved by the Comité d'Evaluation des Registres (French National Committee of Registers) and the InVS (French Institute for Public Health Surveillance).

Results

During the whole study period, a total of 5285 stroke patients were registered. These included 4614 patients with a first-ever event, of whom 2450 were women (53.1%; mean age, 76.4±15.4 years) and 2164 were men (46.9%, mean age: 71.4±14.1 years). Among these patients, 3818 patients (82.7%) had IS, 530 patients (11.5%) had ICH, 148 patients (3.2%) had SAH, and 118 patients (2.6%) had undetermined stroke.

The annual crude incidence rate per 100 000 was 134.2 (95% CI, 130.3–138.1) for the whole study period. Corresponding rate standardized to the European population was 86.6 (95% CI, 83.9–89.3). A lower incidence was observed in women than in men (Table). This lower incidence in women was noted in the age group 45 to 84 years, whereas there was no evidence of sex differences in incidence rates for age groups 35 to 44 and ≥85 years. Conversely, in people aged <35 years, the stroke incidence rate was greater in women.

When considering stroke subtypes, the lower incidence in women was noted for both IS and ICH. In contrast, no sex difference was observed for the incidence of SAH and undetermined stroke.

From 1987 to 2012, there was a slight increase in the incidence of overall stroke (IRR, 1.012; 95% CI, 1.008–1.015; *P*=0.001; Figure 1). This increase was observed in both men (IRR, 1.011; 95% CI, 1.005–1.016; *P*=0.001) and women (IRR, 1.013; 95% CI, 1.007–1.018; *P*=0.001). The lower incidence of stroke in women was constant over time, with a sex IRR ranging between 0.63 and 0.72 depending on the time period (Figure 1).

Consistent results were observed when considering IS only (Figure 2). There was an increase in incidence of overall

Table. Incidence Rates of First-Ever Stroke in Dijon, France, From 1987 to 2012

Incidence Rates (n/100 000/y)															
	Women and Men				Women				Men				IRR		
	n at Risk	n	Rates	95% CI	n at Risk	n	Rates	95% CI	n at Risk	n	Rates	95% CI	IRR	95% CI	*P* Value
Crude incidences rates	3 896 484	4614	134.2	130.3–138.1	2 080 464	2450	111.5	107.0–116.0	1 816 020	2164	166.2	159.1–173.3	0.68	0.64–0.72	<0.001
Standardized Incidence rates*	3 896 484	…	86.6	83.9–89.3	…	…	69.1	65.9–72.2	…	…	110.3	105.5–115.1	…	…	…
Incidence rates by age groups, y															
<35	2 018 574	111	5.5	4.5–6.6	1 038 232	74	7.1	5.6–8.9	980 342	37	3.8	2.7–5.2	1.89	1.27–2.8	0.002
35–44	483 156	142	29.4	24.8–34.6	247 109	71	28.7	22.4–36.2	236 047	71	30.1	23.5–37.9	0.96	0.69–1.33	0.785
45–54	441 412	267	60.5	53.4–68.2	229 089	108	47.1	38.7–56.9	212 323	159	74.9	63.7–87.5	0.63	0.5–0.81	<0.001
55–64	355 278	514	144.7	132.4–157.7	190 608	161	84.5	71.9–98.6	164 670	353	214.4	192.6–237.9	0.39	0.33–0.47	<0.001
65–74	274 966	906	329.5	308.4–351.7	160 906	362	225.0	202.4–249.4	114 060	544	476.9	437.7–518.8	0.47	0.41–0.54	<0.001
75–84	223 242	1608	720.3	685.5–756.4	142 907	924	646.6	605.6–689.6	80 334	684	851.4	788.8–917.7	0.76	0.69–0.84	<0.001
≥85	99 856	1066	1067.5	1004–1134	71 614	750	1047.3	974–1125	28 243	316	1118.9	999–1249	0.93	0.82–1.06	0.296
Incidence rates by mechanisms*															
Ischemic stroke	3 896 484	3818	70.9	68.5–73.4	2 080 464	2019	55.5	52.7–58.3	1 816 020	1799	91.6	87.2–96.0	0.67	0.63–0.72	<0.001
Hemorrhagic stroke	3 896 484	530	10.0	9.1–11.0	2 080 464	274	8.0	6.9–9.0	1 816 020	256	12.9	11.3–14.6	0.65	0.55–0.77	<0.001
Subarachnoid hemorrhage	3 896 484	148	3.8	3.1–4.4	2 080 464	86	3.9	3.1–4.8	1 816 020	62	3.5	2.6–4.4	1.10	0.79–1.53	0.574
Undetermined stroke	3 896 484	118	1.9	1.5–2.3	2 080 464	71	1.7	1.2–2.2	1 816 020	47	2.2	1.5–2.8	0.83	0.57–1.2	0.321

CI indicates confidence interval; and IRR, women/men incidence rate ratio.
*Standardized to European population.

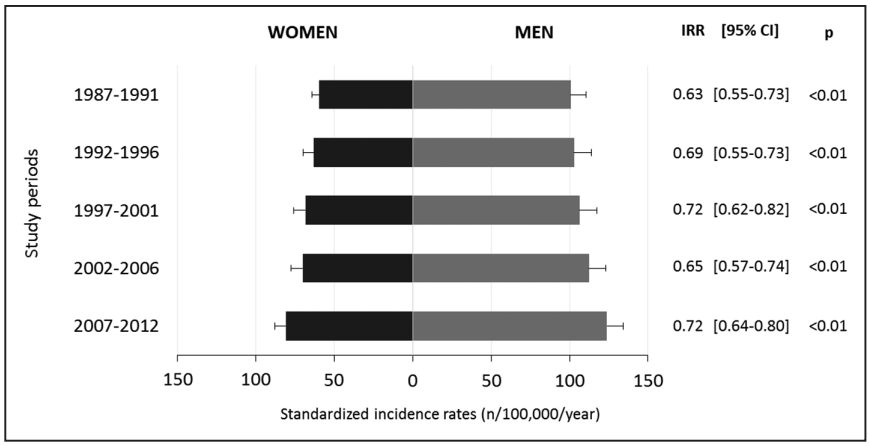

Figure 1. Incidence rates standardized to the European population of first-ever stroke by study periods in men and women. CI indicates confidence interval; and IRR, women/men incidence rate ratio.

IS (IRR, 1.014; 95% CI, 1.009–1.018; *P*=0.001) with the same magnitude in men (IRR, 1.013; 95% CI, 1.007–1.019; *P*=0.001) as in women (IRR, 1.015; 95% CI, 1.009–1.020; *P*=0.001). For ICH, the incidence also increased. Similar changes were noted in men (IRR, 1.022; 95% CI, 1.006–1.039; *P*=0.008) and women (IRR, 1.023; 95% CI, 1.007–1.039; *P*=0.005). Although some variations were noted between study periods, the lower incidence of ICH observed in women remained unchanged with time. Finally, the incidence of SAH increased in women only (IRR, 1.066; 95% CI, 1.034–1.100; *P*=0.001 versus IRR, 1.007; 95% CI, 0.997–1.040; *P*=0.69 in men). As a result, the lower incidence in women noted in the study period 1987 to 1991 vanished with time and tended to reverse in the last study period.

Discussion

This study demonstrated a greater incidence of stroke in men than in women, with consistent results observed in both IS and ICH. In addition, sex differences in stroke incidence remained stable over the past 25 years.

A previous systematic review of population-based studies reported a 33% higher stroke incidence in men, which is similar to our findings when considering the overall study period (32%).[1] The excess in incidence in men in this review was significant for the age band 35 to 84 years, whereas the incidence was similar in both sexes in individuals younger or older than this age band. As noted in our study, the Greater Cincinnati–Northern Kentucky Stroke Study found a higher incidence of stroke in women <35 years of age.[7] The exposure of young women to estrogenic oral contraception, a well-established risk factor for stroke, may contribute to this result.[8] In contrast, the higher prevalence of traditional vascular risk factors in middle-aged men, including the fact that that blood pressure levels have been shown to be greater in men than in women of similar ages,[9,10] probably explains the excessive incidence at this age. Several studies also pointed out that stroke incidence was higher in women >75 or 85 years of age,[11,12] and no sex difference was observed in people ≥85 years of age in our study. A large proportion of strokes at this age are related to atrial fibrillation, and some studies suggested that the risk of atrial fibrillation–related stroke could be greater in women than in men, thus contributing to these findings.[13]

In the present study, the sex gap in stroke incidence remained unchanged during 25 years. This result illustrates a stable excess in the prevalence of vascular risk factors in men compared with women. In addition, the incidence of IS increased in both sexes. This trend was driven by a rise in IS incidence in people aged <55 years, as previously reported in our population-based registry and other studies.[14–19] To account for this result, it has been shown that the prevalence of several vascular risk factors including diabetes mellitus, hypercholesterolemia, and obesity increased in high-income countries. Of note, the

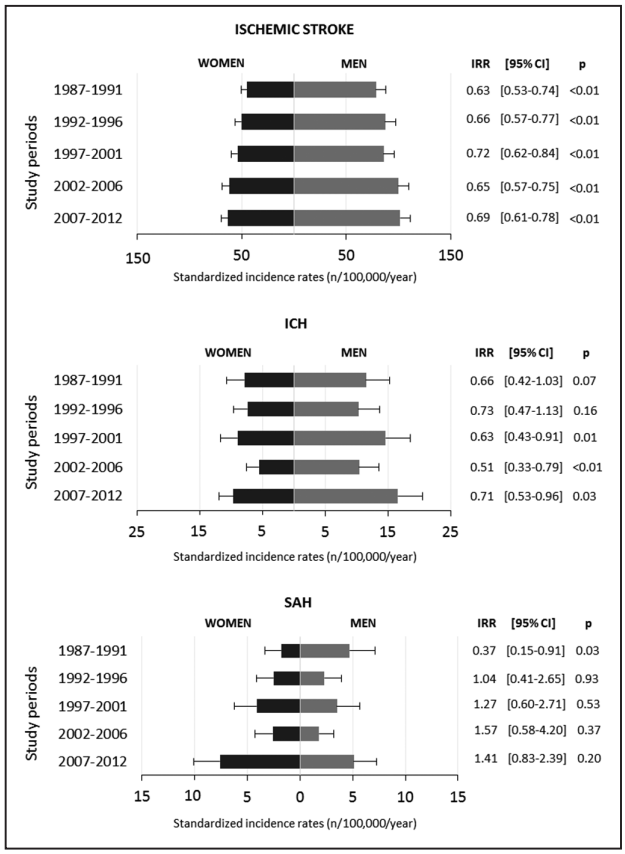

Figure 2. Incidence rates standardized to the European population of first-ever stroke by study periods in men and women, stratified by stroke subtype. CI indicates confidence interval; ICH, intracerebral hemorrhage; IRR, women/men incidence rate ratio; and SAH, subarachnoid hemorrhage.

prevalence of cigarette smoking also increased in France during the 2000s especially in women,[20] contrasting with trends in other western European countries. This could explain the increasing incidence of SAH in women, whereas other authors reported a decreasing trend in Finland, concomitantly with reduced smoking rates.[21] Our results are consistent with the recent observation of the GBD study, which also reported a stable sex gap in stroke incidence between 1990 and 2013 worldwide, including both developed and developing countries.[2]

The major strength of this study is the continuous collection of stroke cases among a well-defined and stable population. However, despite a rigorous methodology to ensure the exhaustive identification of patients, we cannot exclude the possibility that case ascertainment improved with time. For instance, the increased use of brain magnetic resonance imaging in routine practice could have contributed to a more accurate diagnosis of stroke especially in patients presenting with minor symptoms. Nevertheless, to avoid a potential shift from a diagnosis of transient ischemic attack toward one of IS, we used the epidemiological definition of stroke, that is, neurological signs lasting for >24 hours, throughout the whole study period. In addition, better awareness of stroke in the population could have led more patients to seek medical attention over time. Nevertheless, there is no reason to think that such changes in patients' attitudes could have affected our findings about sex differences in stroke incidence. Finally, results about ICH and SAH must be interpreted with cautious because of a limited numbers of cases (530 and 148, respectively).

To conclude, during the study period, the sex gap in stroke incidence did not change except for SAH, and incidence rates increased in both men and women. Despite lower rates, more women than men experience an incident stroke each year because of a longer life expectancy than that in men.

Disclosures

Dr Béjot received honoraria or consulting fees from AstraZeneca France, Daiichi-Sankyo, BMS-Pfizer, Covidiem, Bayer, and MSD France. The other authors report no conflicts.

References

1. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke*. 2009;40:1082–1090. doi: 10.1161/STROKEAHA.108.540781.
2. Barker-Collo S, Bennett DA, Krishnamurthi RV, Parmar P, Feigin VL, Naghavi M, et al; GBD 2013 Writing Group; GBD 2013 Stroke Panel Experts Group. Sex differences in stroke incidence, prevalence, mortality and disability-adjusted life years: results from the Global Burden of Disease Study 2013. *Neuroepidemiology*. 2015;45:203–214. doi: 10.1159/000441103.
3. Lainay C, Benzenine E, Durier J, Daubail B, Giroud M, Quantin C, et al. Hospitalization within the first year after stroke: the Dijon stroke registry. *Stroke*. 2015;46:190–196. doi: 10.1161/STROKEAHA.114.007429.
4. Bennett DA, Brayne C, Feigin VL, Barker-Collo S, Brainin M, Davis D, et al. Development of the Standards of Reporting of Neurological Disorders (STROND) checklist: a guideline for the reporting of incidence and prevalence studies in neuroepidemiology. *Neurology*. 2015;85:821–828. doi: 10.1212/WNL.0000000000001866.
5. WHO. *The World Health Report 2000: Health Systems Improving Performance*. Geneva: WHO; 2000.
6. Eurostat. Revision of the European Standard Population. http://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f. Accessed October 27, 2016.
7. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5.
8. Chan WS, Ray J, Wai EK, Ginsburg S, Ginsburg S, Hannah ME, et al. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med*. 2004;164:741–747. doi: 10.1001/archinte.164.7.741.
9. Wiinberg N, Høegholm A, Christensen HR, Bang LE, Mikkelsen KL, Nielsen PE, et al. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. *Am J Hypertens*. 1995;8(10 pt 1):978–986. doi: 10.1016/0895-7061(95)00216-2.
10. Wagner A, Sadoun A, Dallongeville J, Ferrières J, Amouyel P, Ruidavets JB, et al. High blood pressure prevalence and control in a middle-aged French population and their associated factors: the MONA LISA study. *J Hypertens*. 2011;29:43–50. doi: 10.1097/HJH.0b013e32833f9c4d.
11. Löfmark U, Hammarström A. Evidence for age-dependent education-related differences in men and women with first-ever stroke. Results from a community-based incidence study in northern Sweden. *Neuroepidemiology*. 2007;28:135–141. doi: 10.1159/000102141.
12. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet*. 2005;366:1773–1783. doi: 10.1016/S0140-6736(05)67702-1.
13. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–1691. doi: 10.1161/CIRCULATIONAHA.105.553438.
14. Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, et al. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc*. 2016;5:pii: e003233.
15. Tibæk M, Dehlendorff C, Jørgensen HS, DMSc, MD, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: a registry-based study. *J Am Heart Assoc*. 2016;5:e003158.
16. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781–1787. doi: 10.1212/WNL.0b013e318270401d.
17. Béjot Y, Daubail B, Jacquin A, Durier J, Osseby GV, Rouaud O, et al. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. *J Neurol Neurosurg Psychiatry*. 2014;85:509–513. doi: 10.1136/jnnp-2013-306203.
18. Medin J, Nordlund A, Ekberg K; Swedish Hospital Discharge Register. Increasing stroke incidence in Sweden between 1989 and 2000 among persons aged 30 to 65 years: evidence from the Swedish Hospital Discharge Register. *Stroke*. 2004;35:1047–1051. doi: 10.1161/01.STR.0000125866.78674.96.
19. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70:713–721. doi: 10.1002/ana.22539.
20. Guignard R, Beck F, Richard JB, Lermenier A, Wilquin JL, Nguyen-Thanh V. Tobacco consumption in France in 2014: characteristics and recent trends. *INPES Health Barometer*. http://inpes.santepubliquefrance.fr/CFESBases/catalogue/pdf/1611.pdf. Accessed January 26, 2017.
21. Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2016;87:1118–1123. doi: 10.1212/WNL.0000000000003091.