Temporal Trends in Sex Differences With Regard to Stroke Incidence
The Dijon Stroke Registry (1987–2012)

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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 100000/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.

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. 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. 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 151543 inhabitants). It complies with the defined criteria for conducting ideal incidence stroke studies. Methodology of case ascertainment and adjudication has been extensively described elsewhere. 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). 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. 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
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. 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.

**Ethics**
The Dijon Stroke Registry was approved by the Comité d’Évaluation 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

| Incidence Rates of First-Ever Stroke in Dijon, France, From 1987 to 2012 |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 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 | P Value |
| **Crude incidences rates** | | | | | | | | | | |
| 3896484 | 4614 | 134.2 | 130.3–138.1 | 2080464 | 2450 | 111.5 | 107.0–116.0 | 1816020 | 2164 | 166.2 | 159.1–173.3 | 0.68 | 0.64–0.72 | <0.001 |
| **Standardized incidence rates** | | | | | | | | | | |
| 3896484 | 86.6 | 83.9–89.3 | | | | | | | | | | |
| **Incidence rates by age groups, y** | | | | | | | | | | |
| <35 | 2018574 | 111 | 5.5 | 4.5–6.6 | 1038232 | 74 | 7.1 | 5.6–8.9 | 980342 | 37 | 3.8 | 2.7–5.2 | 1.89 | 1.27–2.8 | 0.002 |
| 35–44 | 483156 | 142 | 29.4 | 24.8–34.6 | 247109 | 71 | 28.7 | 22.4–36.2 | 236047 | 71 | 30.1 | 23.5–37.9 | 0.96 | 0.69–1.33 | 0.765 |
| 45–54 | 441412 | 267 | 60.5 | 53.4–68.2 | 229089 | 108 | 47.1 | 38.7–56.9 | 213233 | 159 | 74.9 | 63.7–87.5 | 0.63 | 0.5–0.81 | <0.001 |
| 55–64 | 355278 | 514 | 144.7 | 132.4–157.7 | 190608 | 161 | 84.5 | 71.9–98.6 | 164670 | 353 | 214.4 | 192.6–237.9 | 0.39 | 0.33–0.47 | <0.001 |
| 65–74 | 274966 | 906 | 329.5 | 308.4–351.7 | 160906 | 362 | 225.0 | 202.4–249.4 | 114060 | 544 | 476.9 | 437.7–518.8 | 0.47 | 0.41–0.54 | <0.001 |
| 75–84 | 223242 | 1608 | 720.3 | 685.5–756.4 | 142907 | 924 | 646.6 | 605.6–689.6 | 80334 | 684 | 851.4 | 788.8–917.7 | 0.76 | 0.69–0.84 | <0.001 |
| ≥85 | 99856 | 1066 | 1067 | 1004–1134 | 71614 | 750 | 1047.3 | 974–1125 | 28243 | 316 | 1118.9 | 999–1249 | 0.93 | 0.82–1.06 | 0.296 |

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

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

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. 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 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.

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, 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. 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.

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 caution 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, Datichi-Sankyo, BMS-Pfizer, Covidiem, Bayer, and MSD France. The other authors report no conflicts.

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Stroke. 2017;48:846-849; originally published online March 8, 2017;
doi: 10.1161/STROKEAHA.116.015913

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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