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Time Trends in Incidence of Pathological and Etiological Stroke Subtypes during 16 Years: The Erlangen Stroke Project

Peter L. Kolominsky-Rabas[a] Silke Wiedmann[b] Michael Weingärtner[a]
Thomas G. Liman[c] Matthias Endres[c] Stefan Schwab[d] Michael Buchfelder[e]
Peter U. Heuschmann[b, f]

[a]Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen-Nürnberg, [b]Institute of Clinical Epidemiology and Biometry, Comprehensive Heart Failure Center, University of Würzburg, Würzburg, [c]Department of Neurology, Center for Stroke Research, German Center for Neurodegenerative Diseases (DZNE), German Center for Cardiovascular Research (DZHK), Partner Site, Charité – Universitätsmedizin Berlin, Berlin, [d]Department of Neurology, [e]Department of Neurosurgery, University Hospital Erlangen, Erlangen, and [f]Clinical Trial Center Würzburg, University Hospital Würzburg, Würzburg, Germany

Key Words
Stroke · Epidemiology · Incidence · Time trends · Register

Abstract
Background: Population-based data, which continuously monitors time trends in stroke epidemiology are limited. We investigated the incidence of pathological and etiological stroke subtypes over a 16 year time period. ***Methods:*** Data were collected within the Erlangen Stroke Project (ESPro), a prospective, population-based stroke register in Germany covering a total study population of 105,164 inhabitants (2010). Etiology of ischemic stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. ***Results:*** Between January 1995 and December 2010, 3,243 patients with first-ever stroke were documented. The median age was 75 and 55% were females. The total stroke incidence decreased over the 16 year study period in men (Incidence Rate Ratio 1995–1996 vs. 2009–2010 (IRR) 0.78; 95% CI 0.58–0.90) but not in women. Among stroke subtypes, a decrease in ischemic stroke incidence (IRR 0.73; 95% CI 0.57–0.93) and of large artery atherosclerotic stroke (IRR 0.27; 95% CI 0.12–0.59) was found in men and an increase of stroke due to small artery occlusion in women (IRR 2.33; 95% CI 1.39–3.90). ***Conclusions:*** Variations in time trends of pathological and etiological stroke subtypes were found between men and women that might be linked to gender differences in the development of major vascular risk factors in the study population.

Background

Due to the ageing population, the absolute number of stroke patients is expected to increase substantially in the next decades if age-specific incidence rates remain stable [1, 2]. Simulation studies showed that the absolute number of stroke patients can be reduced if effective preventive measures in the population were applied for primary

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E-Mail karger@karger.com
www.karger.com/ned

Peter L. Kolominsky-Rabas, MD, PhD, MBA, Erlangen Stroke Project (ESPro) – National Information System of the Federal Health Monitoring, Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health Friedrich-Alexander University of Erlangen-Nürnberg Schwabachanlage 6 DE–91052 Erlangen (Germany), E-Mail peter.kolominsky@uk-erlangen.de

or secondary stroke prevention [3]. Therefore, data monitoring time trends in the incidence and underlying pathomechanisms of stroke are useful to inform health policy decision makers about the effectiveness of prevention strategies in the population. Previous studies on time trends in stroke incidence during the last years reported conflicting results [4–9]. Population-based data continuously monitoring incidence of etiological stroke subtypes within the same source population over a time span of more than one decade are scarce. In addition, time trends related to the incidence of ischemic stroke that can be obtained using an established mechanism-based classification scheme such as the Trial of Org 10172 in Acute Stroke Treatment criteria (TOAST) [10] are lacking.

We investigated 16-year time trends in the incidence of pathological and etiological stroke subtypes using a standardized pathological and etiological mechanism-based classification system within a population-based stroke register. The incidence of stroke subtypes within the same study population in Germany was continuously monitored.

Material and Methods

The Erlangen Stroke Project (ESPro) is an ongoing prospective community-based stroke register in Germany, which has continuously monitored stroke incidence in a study population of 105,164 inhabitants (census 2010) since 1994. The characteristics of the study population, methods of assessment, and investigations have been described in detail elsewhere [11].

Data Collection

From January 1995 to December 2010, all hospitalized and nonhospitalized patients in the study area with suspected fatal or nonfatal stroke or transient ischemic attack were identified. To ensure completeness of case ascertainment, standardized criteria were applied with details published previously [11, 12]. To identify patients admitted to hospitals, daily checks of hospital admission and discharge records were made in the study area. In addition, nursing and residential homes were checked for identifying nonhospitalized stroke patients. For an accurate estimate of the number of nonfatal strokes that were managed outside the hospital, the general practitioners in the community were contacted regularly. There were no major changes in case ascertainment methods during the study period. Special trained study nurses and research assistants collected all data prospectively following standardized operating procedures that were stable over the whole documentation period.

Data Definition

Stroke diagnosis was defined by a study clinician according to the criteria of the World Health Organization [13]. Patients with first-ever-lifetime-stroke were included in the present study [14]. Classification of pathological stroke subtype (ischemic stroke [IS], primary intracerebral hemorrhage [PICH], and subarachnoid hemorrhage [SAH]) was established by means of brain imaging (CT or MRI scan) or necropsy examination. All patients with stroke in whom imaging or post-mortem examination could not be performed or in whom the results of the brain imaging were unknown were classified as unspecified stroke [UNS]. For determination of etiological subtype of ischemic stroke, the original TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria were used [10] with details of evaluation of TOAST classification in the ESPro described previously [12]. Categories of the TOAST classification are large-artery atherosclerosis (LAA), including large-artery thrombosis and artery-to-artery embolism; cardioembolism (CE); small artery occlusion (SAO); stroke of other determined cause (OC); and stroke of undetermined cause (UND). The ratings were performed by trained staff considering the results of all investigations and the neurological examination.

Statistical Analysis

The source population of the ESPro was estimated based on data from the constantly updated official population register of Erlangen. Crude incidence rates were calculated for age group, sex, pathological and etiological stroke subtypes; sex and stroke subtype incidence rates were age-adjusted to the standard European population [15]. Data were reported in two-year time intervals. To enable comparisons, time trends during the 16 year observation period were compared with the first period (1995–1996) by calculating Incidence Rate Ratios (IRR); 95% CI for the direct standardized IRR, calculated by the delta method [16]. Five patients with unknown sex were excluded. The TOAST classification was performed by specifically trained raters considering the results of all diagnostic investigations and the neurological examination. For testing inter-observer reliability of the TOAST classification, twenty randomly selected patients were classified by two independent raters between 1995 and 1998 [12] and additionally forty patients after 1999. Inter-observer reliability of classification among raters was good for both time intervals (unweighted κ 0.65, 95% CI 0.35–0.96 and 0.63, 95% CI 0.43–0.83, respectively). Statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, N.C., USA).

Ethics

The design of the study was approved by the local ethics committee. Patients or their legal representatives gave their written informed consent to participate.

Results

Between January 1995 and December 2010, 3,243 patients with first-ever stroke were registered. The median age was 75 years (Interquartile range 66–82), 1,787 (55%) were females. Changes of the source population regarding socio-demographic characteristics, and stroke subtype over the 16-year study period by sex are shown in online supplementary table A (for all online suppl. material, see www.karger.com/doi/10.1159/000371353).

Table 1. Incidence rate ratio (IRR) and corresponding 95% confidence interval between incidence rates adjusted to the European population 1995–1996 as reference

	1997–1998		1999–2000		2001–2002		2003–2004		2005–2006		2007–2008		2009–2010	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total	0.94 (0.76–1.16)	1.00 (0.83–1.22)	1.07 (0.87–1.31)	0.97 (0.80–1.19)	0.89 (0.72–1.10)	0.72 (0.58–0.89)	0.79 (0.63–0.98)	0.95 (0.78–1.16)	0.90 (0.73–1.11)	0.97 (0.79–1.18)	0.99 (0.81–1.21)	0.81 (0.66–1.00)	0.72 (0.58–0.90)	0.90 (0.74–1.10)
Stroke subtype														
CI	0.94 (0.74–1.19)	1.11 (0.89–1.39)	1.11 (0.89–1.38)	1.11 (0.89–1.39)	0.89 (0.70–1.13)	0.75 (0.58–0.95)	0.80 (0.63–1.02)	1.01 (0.81–1.27)	0.95 (0.76–1.20)	1.04 (0.83–1.30)	0.99 (0.79–1.24)	0.82 (0.64–1.03)	0.73 (0.57–0.93)	0.97 (0.78–1.22)
PICH	0.86 (0.47–1.55)	0.62 (0.35–1.10)	1.12 (0.64–1.97)	0.48 (0.26–0.88)	0.90 (0.50–1.62)	0.56 (0.33–0.96)	0.73 (0.40–1.33)	0.91 (0.55–1.49)	0.75 (0.42–1.36)	0.37 (0.19–0.70)	0.94 (0.54–1.65)	0.53 (0.30–0.93)	0.74 (0.41–1.32)	0.68 (0.40–1.16)
SAH	1.12 (0.34–3.70)	1.32 (0.40–4.39)	0.73 (0.20–2.72)	1.36 (0.41–4.48)	0.73 (0.20–2.71)	1.26 (0.37–4.24)	1.16 (0.35–3.85)	0.90 (0.24–3.44)	0.87 (0.25–3.04)	2.95 (1.03–8.42)	0.96 (0.29–3.20)	1.53 (0.48–4.92)	0.63 (0.16–2.41)	0.90 (0.25–3.20)
UNS	1.17 (0.43–3.16)	0.70 (0.34–1.44)	0.37 (0.10–1.44)	0.50 (0.23–1.11)	1.01 (0.36–2.81)	0.57 (0.26–1.24)	0.48 (0.14–1.69)	0.42 (0.16–1.11)	0.40 (0.12–1.41)	0.76 (0.35–1.65)	1.11 (0.43–2.90)	1.14 (0.57–2.27)	0.68 (0.24–1.94)	0.73 (0.35–1.50)
*TOAST subtype**														
LAA	0.60 (0.32–1.13)	0.80 (0.36–1.80)	0.64 (0.34–1.19)	1.13 (0.52–2.45)	0.59 (0.32–1.10)	0.97 (0.42–2.20)	0.42 (0.21–0.85)	0.95 (0.42–2.14)	0.74 (0.41–1.32)	0.95 (0.43–2.13)	0.73 (0.41–1.30)	0.82 (0.34–1.96)	0.27 (0.12–0.59)	0.40 (0.15–1.04)
CE	1.32 (0.79–2.21)	1.01 (0.68–1.51)	1.43 (0.87–2.36)	0.63 (0.40–1.00)	0.88 (0.51–1.53)	0.48 (0.29–0.77)	1.12 (0.66–1.90)	0.65 (0.43–1.00)	1.26 (0.76–2.08)	0.79 (0.51–1.21)	0.88 (0.51–1.51)	0.47 (0.30–0.75)	0.93 (0.55–1.56)	0.74 (0.48–1.13)
SAO	1.01 (0.63–1.64)	1.98 (1.16–3.37)	1.32 (0.84–2.06)	1.88 (1.11–3.20)	0.94 (0.58–1.51)	1.34 (0.75–2.37)	0.85 (0.52–1.38)	1.59 (0.92–2.75)	0.99 (0.62–1.59)	1.88 (1.12–3.16)	1.30 (0.84–2.02)	2.11 (1.25–3.56)	0.97 (0.61–1.54)	2.33 (1.39–3.90)
UND	0.85 (0.55–1.32)	0.85 (0.59–1.22)	1.08 (0.72–1.62)	1.08 (0.76–1.53)	0.98 (0.65–1.48)	0.67 (0.45–0.98)	0.88 (0.58–1.34)	1.14 (0.81–1.61)	0.98 (0.65–1.46)	1.04 (0.73–1.48)	1.06 (0.71–1.56)	0.75 (0.52–1.09)	0.76 (0.50–1.17)	0.86 (0.60–1.23)

Frequency of Stroke Subtypes

The distribution of pathological subtypes was as follows: ischemic stroke (IS) 2,582 (79.7%); primary intracerebral hemorrhage (PICH) 394 (12.2%); subarachnoid hemorrhage (SAH) 96 (3.0%), and 166 (5.1%) were of unspecified stroke (UNS).

Overall, it was possible to classify ischemic stroke etiology according to the TOAST classification in 2,486 out of 2,582 patients with IS (96.3%). The distribution of etiological ischemic stroke subtypes of patients being classified was as follows: LAA 246 (9.9%); CE 609 (24.5%); SAO 654 (26.3%); OC 43 (1.7%); UND 934 (37.6%) of patients with OC ischemic stroke was caused by the following reasons: fibro-muscular dysplasia 9 (20.9%); dissection 11 (25.6%); thrombotic disorders 8 (18.6%); migraine 2 (4.7%); vasculitis 5 (11.6%); other causes 8 (18.6%).

Stroke Incidence

Biannual stroke incidence rates per 100,000 age-adjusted to the European population are presented in online supplementary table B. Time trends in age-standardized incidence rates are shown in table 1. Total stroke incidence decreased over the 16 year study period in men (incidence rate ratio 1995–1996 vs. 2009–2010 (IRR) 0.72; 95% CI 0.58–0.90) but not in women (IRR 0.90; 95% CI 0.74–1.10). Among pathological stroke subtypes, a decrease in ischemic stroke incidence was found in men (IRR 0.73; 95% CI 0.57–0.93). Incidence of LAA stroke decreased in men (IRR 0.27; 95% CI 0.12–0.59) and incidence of SAO increased in women (IRR 2.33; 95% CI 1.39–3.90).

Discussion

In our study a moderate reduction in overall stroke incidence was found for men but not in women over the 16 year study period. Incidence of ischemic stroke decreased in men, with no other major changes in incidence of different stroke subtypes observed. Regarding ischemic stroke etiology, a reduction of incidence of LAA was seen in men and an increase of SAO in women.

A systematic review on world-wide stroke incidence trends found a decrease in overall age-adjusted stroke incidence rates over the last forty years in the developed countries [17]. For the last decade, however, data on temporal trends of age- and sex-adjusted stroke incidence in European populations is limited [1]. Moreover, the estimation of time-trends across different population-based registers might be difficult as these studies are heteroge-

neous in a number of factors affecting stroke incidence in the local population such as geographical region, ethnic group diversity or risk factor distribution in the general population. Population-based studies reporting time trends in stroke incidence in the same source population since the mid-1990s demonstrated decreasing rates in the United Kingdom [4–6], the United States [7], New Zealand [8] in mainly white as well as in multi-ethnic populations. No changes in stroke rates however were observed in black US Americans [7], while an increase in incidence was found in 'pacific people' in New Zealand [8], France [9] and some parts of Eastern Europe [18, 19]. There are possible explanations for these differences in time trends of age-adjusted incidence rates of population-based studies during the last years. A higher age-adjusted annual stroke incidence rate was found in stroke registers that reported a decrease of stroke incidence over time [5, 6, 8]. Compared to our data, that might indicate that our population already reached a 'floor' effect in stroke incidence. Major ethnic differences of source populations may also contribute to this heterogeneity in variations of stroke risk over time as registers including multi-ethnic populations such as the SLSR or the ARCOS reported significant ethnic group disparities in incidence trends [5, 8].

Data from previous population-based studies on time trends regarding pathological subtypes suggest a decrease in primary intracerebral hemorrhage (PICH) during the last 20 years in high-income countries [17]. However, in line with our findings, no major time trends in PICH incidence was found in the white SLSR population and in the Dijon Register between 1985 and 2004 [4, 20]. The lacking decrease in incidence of PICH in the ESPro from 1995 to 2010 might be caused by stable prevalence rates of hypertension in the population, one of the major risk factors for PICH. In a recent review of representative cross-sectional surveys on vascular risk factors in North America and Europe, Germany is considered to be one of the regions with the highest prevalence of hypertension [21] that was also confirmed by recent data from the general population [21, 22]. In line with our findings, time trends of subarachnoid hemorrhage (SAH) are showing stable incidence rates during the last decades [17].

Regarding the etiology of ischemic stroke subtypes, we observed in our study population a reduction of LAA incidence in men and an increase of SAO in women. To the best of our knowledge, data on time trends in incidence of etiological stroke subtypes from population-based studies using an established mechanism-based classification system such as the TOAST classification are lacking so far. Improved primary preventive treatment and a healthier lifestyle during the last two decades in our population might account for the finding in men. For example, an increase in the uptake of statin therapy was observed in the recent years as well as a decrease of smoking in the general population [23, 24]. The higher incidence of SAO in women might be caused by an increase in the prevalence of risk factors for this subtype such as hypertension, which is highly prevalent in the general older aged population with rather stable prevalence rates in Germany [22]. The life expectancy of people from the source population increased during the study period. However, as we are reporting age-standardized rates, the effect of increasing age in our source population should be controlled for. Similar to other population-based stroke registers [20], we could not observe an increase in the rate of cardioembolic strokes over time. As cardioembolic stroke due to atrial fibrillation occurs often in older age groups, especially in females, this might be explained by the fact that there were no major changes in the median age at stroke onset in the register.

Our study has limitations. One limitation represents the small sample size of our source population, which resulted in wide confidence intervals of the respective estimates. In addition, due to the design of the study we were not able to link the incidence data with data on treatment and control of major vascular risk factors from the general local population. No data were available for assessing potential time trends in the use of statins, antithrombotic agents or carotid surgery in the general population. We cannot exclude that changes in the used diagnostic techniques over the 16 year time period might have contributed to some of our findings; for example, due to the wider availability and the better diagnostic accuracy of diagnostic techniques such as extra-cranial imaging. Finally, some limitations of the mechanism-based TOAST classification system need to be addressed, such as the high rates of undefined stroke due to missing distinctions between undefined and concurrent etiology as well as the noninclusion of new pathophysiological and diagnostic knowledge. Novel adaptations of the TOAST criteria have been proposed, which were not available at the time the study was initiated [25, 26].

Conclusion

Variations in time trends of pathological and etiological stroke subtypes were found between men and women that might be linked to gender differences in the development of major vascular risk factors in our population.

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