Age–Period–Cohort Analysis of Stroke Incidence in Dijon From 1985 to 2005

Meheni Khellaf, MD; Catherine Quantin, MD; Philippe d’Athis, PhD; Maniane Fassa, PhD; Valérie Jooste, PhD; Marie Hervieu, MD; Maurice Giroud, MD; Yannick Béjot, MD

Background and Purpose—Variations in stroke incidence could be explained by changes in vascular and environmental factors that affect the risk of stroke and changes in risk factors that are present in early life. The aim of this study was to identify and measure the effects of 3 interrelated factors, age, calendar period of stroke onset, and birth year cohort, on the incidence rates of stroke from 1985 through 2005.

Methods—Age–period–cohort models were used to analyze stroke incidence in Dijon from 1985 to 2005 from a population-based registry that collects data on all stroke patients whatever the type of management, in the public hospital, private hospitals, or at home, in the population of Dijon (150 000 inhabitants).

Results—For ischemic stroke, the incidence rose with time in men depending not only on age, but also on the period and cohort effects (P = 0.017). For women, the incidence only depended on age (P < 0.001; incidence rate ratio, 1.085; 95% CI, 1.081 to 1.089). For hemorrhagic stroke, the rise in the incidence with time depended only on age in men, whereas in women, it depended on age, period, and cohort effects (P = 0.019).

Conclusions—Age, birth cohort, and calendar period contain relevant information to define and explain trends in stroke incidence rates over a long period. (Stroke. 2010;41:00-00.)

Key Words: age ■ cohort ■ incidence ■ period ■ stroke

Understanding of the natural history of stroke is improving in Western1–3 as well as in developing countries.4 It is therefore possible to identify geographic disparities.5,6

Some studies have already observed a delay in the age at stroke onset: 3 years in both men and women in Sweden,7 2 years in New Zealand,8 and 1.5 years only in men in the United Kingdom.9 However, these results on the delay in the age at stroke onset were obtained comparing the mean age of stroke onset in 2 remote periods without taking into account the variability in trends in the incidence of stroke over time. It therefore seems necessary to take into account the evolution in morbidity over time to explain this possible delay in the age at stroke onset.

We used the age–period–cohort model methods proposed by Clayton and Shiffers10 to describe variations in the stroke incidence rate in Dijon from 1985 to 2005 simultaneously taking into account the effect of age, calendar period of stroke onset, and birth cohort.

Materials and Methods

Study Area and Population

The study population comprised all residents of the town of Dijon in eastern France. According to the national census, the population of Dijon was 146 723 in 1990 and 150 138 in 1999. The number of individuals aged ≥80 years increased by 7.3% between 1985 and 2005.

Case Ascertainment

The detailed methodology of case ascertainment has already been described elsewhere.11,12 Briefly, multiple overlapping sources of information were used to ensure the complete collection of cases: (1) the emergency rooms as well as all the clinical and radiological departments of Dijon University Hospital with a diagnosis of stroke made by 1 neurologist; (2) the emergency rooms and all the clinical departments of the 3 private hospitals of the city and its suburbs with diagnosis made by private neurologists working in these establishments; (3) the patient’s home or the nursing homes of the city with diagnosis assessed by the 250 general practitioners with the help of an outpatient clinic with either a public or private neurologist; (4) the 3 private radiological centers, where the medical records were reviewed to identify missed cases; (5) the ultrasound Doppler centers, where medical records were reviewed; and (6) the death certificates with stroke as the underlying cause of death obtained from the local Social Security Bureau that is responsible for registering all deaths in the community. All the collected death certificates were checked by a member of our team to include only the patients who died from stroke.3,6

To assess the quality and the validity of the registry, an external audit check has been performed every 4 years by the National Medical Research Institute.

Received June 1, 2010; final revision received July 29, 2010; accepted September 2, 2010.

From the Dijon Stroke Registry (Inserm, InVS; M.K., M.H., M.G., Y.B.), University Hospital and Faculty of Medicine of Dijon, University of Burgundy, Burgundy, France; Laboratoire d’Informatique Médicale (M.K., C.Q., P.d.A., M.F.), University Hospital and Faculty of Medicine of Dijon, University of Burgundy, Burgundy, France; and the Dijon Cancer Registry (Inserm, InVS; V.J.), University Hospital and Faculty of Medicine of Dijon, University of Burgundy, Burgundy, France.

Correspondence to Maurice Giroud, MD, CHU–3 Rue du Faubourg Raines–21000 Dijon, France. E-mail maurice.giroud@chu-dijon.fr
© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.110.592147
Diagnosis of Stroke Subtype and Classification
Stoke was defined according to the World Health Organization recommendations and the International Classification of Diseases. The stroke subtype was always diagnosed on a clinical basis completed by cerebral imaging, 2-dimensional echocardiography, carotid and vertebral ultrasonography as well as standard blood and urine tests. Since 1985, we grouped ischemic stroke as follows: (1) ischemic strokes from lipohyalinosis of small arteries, so-called lacunar infarct defined as a stroke presenting 1 of the classical lacunar syndromes and confirmed by a small (≤15 mm in diameter) subcortical infarct on brain CT scan or MRI in the absence of any other morphological cause of ischemic stroke found in the neuroimaging examination; (2) ischemic stroke from cardiac embolism due to either atrial fibrillation diagnosed on electrocardiogram or Holter electrocardiogram, or to valve disease, patent foramen ovale, or spontaneous intracavitary thrombus on echocardiography; and (3) all other ischemic strokes characterized by focal cortical symptoms and cortical infarct on a large vascular territory on CT or MRI. Intracerebral hemorrhagic grouped spontaneous intracerebral hemorrhage and subarachnoid hemorrhage.

Prestroke Vascular Risk Factors and Treatments
We collected prestroke vascular risk factors using the same methodology throughout the study period. Hypertension was defined by a history of known hypertension (≥140/85 mm Hg) or antihypertensive treatment. Diabetes mellitus was recorded if a glucose level of ≥7.8 mmol/L had been reported in the medical record or if the patient was on insulin or oral hypoglycemic agents. Hypercholesterolemia was defined by total cholesterol 5.7 mmol/L or if the patient was under lipid-lowering therapy. Alchohol intake (≥1 glass per day), smoking was defined as 1 cigarette per day. Antiplatelet agents were recorded.

Statistical Analysis
The incidence rates were calculated using the population of Dijon intramuros according to the census of 1990 and 1999. Because the rates for those <18 and ≥94 years were too low to be meaningful for analysis, we calculated incidence rates according to 11 age classes of 7 years (18 to 24, 25 to 31, 32 to 38, 39 to 45, 46 to 52, 53 to 59, 60 to 66, 67 to 73, 74 to 80, 81 to 87, and 88 to 94), in 3 periods of 7 years (1985 to 1991, 1992 to 1998, and 1999 to 2005), the period 1985 to 1991 being the reference, and in 15 cohorts of 7 years (middle year of cohort: 1890, 1897, 1904, 1911, 1918, 1925, 1932, 1939, 1946, 1953, 1960,1967, 1974, 1981, and 1988).

The incidence rate was measured as a function of age, period, and birth cohort. The advantage of this method is that the age effect expresses the way of life, physiological, biological, behavioral factors, and vascular risk factors; the period effect reflects the environmental factors that act around stroke onset, including the effects of primary prevention and new medical care procedures, whereas the birth cohort effect reflects the characteristics of each generation and includes risk factors and exposure to environmental factors that are present in early life.

Thus, we simultaneously considered age, period, and birth cohort as the 3 variables affecting the risk of disease assuming, as suggested by Clayton and Schifflers, that the interaction between age and period corresponds to the birth cohort, the Age-Period-Birth cohort model will be close to the age–period–cohort model.

The combined effects of age, period, and cohort on stroke onset were studied (1) by sex and mechanism; and (2) globally (any mechanism) to compare our results with the literature.

Each analysis used a specific form of the following age–period–cohort model: \( \gamma_{ijc} = \mu + \alpha_i + \beta_j + \delta_{ij} + \epsilon_{ijc} \) where \( \gamma_{ijc} \) is the function of time, \( \mu \) the global mean value of \( \gamma_{ijc} \), \( \alpha_i \) the effect for the class of age \( i \), \( \beta_j \) the effect for the period \( j \), and \( \delta_{ij} \) the effect for cohort \( c \).

This model has 4 forms: (1) the “age–drift” model, in which drift means that the period is to take the values 1, 2, 3, ..., which enables us to consider linear variations over time for the logarithm of incidence rate, these variations being similar for all age groups; (2) the “age–period” model (AP); (3) the “age–cohort” model (AC); and (4) the model including “age–period–their interaction” (AP+AC). The parameters of each model were estimated with a Poisson regression using the STATA Gauss software package to maximize the likelihood. Pearson residuals were calculated and analyzed to test the assumptions of the models. Every model was evaluated by its deviance from the null model. We compared, using differences in deviances, the models “age + drift,” AP, age + cohort, and AP + A*C with the model “age only” and then with the higher level models. When the AP + A*C model appeared significantly better than the other models, we grouped ages into 18 to 59, 60 to 80, and 81 to 94 years to distinguish between the evolution of stroke incidence in young, middle-aged, and old patients. Finally, incidence curves were drawn for each model using a logarithmic scale.
Results

From 1985 to 2005, we observed within the population of Dijon 3293 strokes comprising 2936 cerebral infarcts (1416 men and 1520 women) and 357 hemorrhagic strokes (173 men and 184 women).

Incidence Rates for Ischemic Strokes

The incidence was higher in men. In men <60 years of age, the annual incidence increased with time by 2.9%, whereas the incidence remained stable in women of any age (Figure 1).

In men, the age + period + interaction model was significantly better than the age model ($P = 0.017$) and than all other models (Table 1). Therefore, in men, the incidence of ischemic stroke did not vary either with the period or with the cohort but increased with age (incidence rate ratio [IRR], 1.085; 95% CI, 1.081 to 1.089).

Incidence Rates for Hemorrhagic Strokes

The incidence rate increased with age, even more in men than in women (Figure 2). In women <60 years of age, the incidence rate was lower in the period 1999 to 2005 than in the period 1985 to 1991 (annual decrease of 8%). Between 60 and 80 years, the rate remained stable in both men and women. In women >80 years of age, the rate of incidence was higher in the period 1999 to 2005 than in the period 1985 to 1991 (annual increase of 5.1%) and remained stable in men >80 years of age.

In men, the age + period + interaction model was not significantly better than the age model ($P = 0.407$) and neither were the age + drift ($P = 0.882$), age + period ($P = 0.310$), and age + cohort ($P = 0.334$) models compared with the age model (Table 3). Therefore, in men, the incidence of hemorrhagic stroke did not vary with either period or cohort, but it increased with age (IRR, 1.085; 95% CI, 1.075 to 1.096).

In women, the age + period + interaction model was significantly better than the age model ($P = 0.019$) than the age model, but the age + drift ($P = 0.816$), age + period ($P = 0.767$), and age + cohort ($P = 0.311$) models were not. Therefore, in women, the incidence of hemorrhagic stroke changed with the period but differently according to age: from 18 to 59 years, the incidence declined at 8% per year (IRR, 0.92; 95% CI, 0.87 to 0.98); in patients from 60 to 80 years, the incidence was stable (IRR, 0.98; 95% CI, 0.945 to 1.016); and in patients from 81 to 94 years, the incidence rose at 5.1% per year (IRR, 1.051; 95% CI, 1.009 to 1.094). Table 4 shows for women aged from 18 to 59 years that the incidence rate decreased significantly by 69% between 1985 to 1991 and 1992 to 1998 and by 58% between 1985 to 1991 and 1999 to
2005. The rate in women aged from 81 to 94 years rose from 1985–1991 to 1999–2005 (IRR, 2.17) and 1999 to 2005 (IRR, 2.42). In women aged from 60 to 80 years, the rates remained stable.

Incidence Rates for All Strokes Combined

To permit comparisons with the literature, we present the results obtained for all mechanisms of stroke.

In men, the age-period interaction model was significantly better \( (P=0.028) \) than the age model (but the age-drift \( (P=0.583) \), age-period \( (P=0.994) \), and age-cohort \( (P=0.068) \) models were not). Therefore, the incidence of stroke changed with the period differently according to age and moderately as shown by the following: the IRR based on 1985 to 1991 differed from 1 in 1992 to 1998 only for the patients aged from 67 to 73 years: 1.35 (95% CI, 1.02 to 1.78), those from 74 to 80 years: 0.67 (0.53 to 0.86), and those from 81 to 87 years: 1.48 (1.11 to 1.97). Similarly, the IRR differed from 1 in 1999 to 2005 only for the patients aged from 74 to 80 years: 0.74 (0.59 to 0.94).

In women, the age-period interaction model was significantly better \( (P=0.028) \) than the age model (but the age-drift \( (P=0.429) \), age-period \( (P=0.086) \), and age-cohort \( (P=0.272) \) models were not). Therefore, like in men, the incidence of stroke changed with periods differently according to age and moderately too: the IRR based on 1985 to 1991 differed from 1 in 1992 to 1998 only for the patients aged from 81 to 87 years: 1.21 (0.98 to 1.50) and in 1999 to 2005 only for the patients aged from 60 to 66: 1.68 (1.02 to 2.77) or from 81 to 87 years: 1.25 (1.01 to 1.55).

Discussion

The age-period–cohort model, used to describe variations in incidence rates over the years by sex and mechanism,\(^{11–13}\) presents several advantages.

The interest of the age-period–interaction model is to describe variations in incidence for stroke in men and women according to age, birth cohort, and period. This means that when explaining trends in rates over the years, we can take into account an interaction between age and period after adjustment for period and age effects.\(^{10–13}\)

Therefore, for ischemic stroke, we observed no change in incidence with period in men and women >60 years of age. However, in men <60 years of age, the incidence increased from 1985 to 2005 with combined effects for age, cohort, and period. For women, only age influenced the incidence rates.

We may explain the effects of age and period by the fact that men are not as sensitive to the prevention of vascular risk factors as women.\(^{15}\) In men, the prevalence of blood hypertension, tobacco, and alcohol abuse is greater than in women and the diagnosis and treatment of vascular risk factors occur later in men than in women.\(^{15}\) The cohort effect may be explained by the environmental conditions of early life such as the nutritional status of the mother during pregnancy, influenza epidemics, the weight and the head circumference of the newborn, and the possible effects of the first and second world wars.

For hemorrhagic stroke, we observed a significantly greater age of stroke onset only in women. The incidence of hemorrhagic stroke in women >80 years of age rose between 1985 and 2005 with combined effects for age, period, and cohort. Age and period effects may be related to the longer life expectancy in women.\(^{15}\) Second, the risk of cerebral hemorrhage rises with age through blood hypertension\(^{16}\) and vascular aging induces amyloid angiopathy, the second major risk for cerebral hemorrhage in the elderly.\(^{17}\) The increase in hemorrhagic stroke incidence could also be explained by the improved diagnosis of small hemorrhagic stroke due to MRI with easier access for the elderly. However, this hypothesis is not the main explanation because we should have observed a rise in the incidence rate of hemorrhagic stroke in both men and women and at any age.

Moreover, the decrease (approximately 60%) in the incidence of hemorrhagic stroke for women <60 of age from 1985 to 2005 can be explained by better primary prevention.
in young women through better control of arterial hypertension, the leading major vascular risk factor for hemorrhagic stroke. The major place of blood hypertension is well demonstrated in our population-based study as well as in studies using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Therefore, this study supports the hypothesis that hemorrhagic stroke occurs at a more advanced age in women and agrees with the hypothesis of a natural delay in disease occurrence at old ages, resulting from medical advances. This was described in Fries theory of morbidity compression, in which the morbidity curve follows the survival curve.

Other hypotheses can explain the relationship between disease and survival at old ages. Kramer suggested that the age at onset of a disease remained the same but that the duration of survival with the disease had increased. By pushing back the time of death, more severe states were reached; this phenomenon is called “the pandemic of mental disorders, chronic diseases and disabilities.” Such hypotheses give a rather negative view of aging. Manton suggested that the increase in life expectancy is partially explained by the slower progression of chronic diseases. The incidence is the same but the duration of the disease increases, leading to an increase in prevalence; moreover, on average, the affections are less severe and mortality decreases. This is the “dynamic equilibrium” hypothesis.

Compared with usual stroke incidence studies, our study highlights the fact that for ischemic stroke, the rise in the incidence rates with time in men depends on age, but also on period and cohort effects, whereas for hemorrhagic stroke in women, the rise in incidence depends on the 3 parameters. This fact reflects the effects of the environmental factors present in early life and around the time of stroke onset combined with the patient’s vascular risk factors. Second, this study was able to demonstrate the delay in the age of hemorrhagic stroke onset in women.

Our study presents limitations related to imaging and coding practices. All diagnoses of stroke subtypes were performed with a systematic CT scan, which is not able to detect small cerebral hemorrhages contrary to MRI (performed in nearly 25% of the cases). However, the underestimation of the incidence rate of hemorrhagic stroke cannot explain the biphasic trends observed only in women. Differences between the multiple revisions of the International Classification of Diseases codes for the stroke diagnosis codes 430 through 438 were small. Changes in coding practices concerned only the identification of ischemic stroke subtypes but not the identification of ischemic and hemorrhagic strokes, the 2 mechanisms studied in our work.

The strength of our study lies in 2 facts: it is based on a stable population with a well-identified medical and research team and long-term observations; and it uses the age–period–cohort model, which gives robust results for incidence rates by sex and mechanism. However, it contrasts with studies that use a model without age, period, and cohort procedures, because it contains information to describe and explain variations in stroke incidence trends.

### Acknowledgments
We thank Professor Michel Velten from the Epidemiology Laboratory, Faculty of Medicine, University of Strasbourg, for his valuable contribution to the article and Philip Bastable for his review of the English.

### Disclosures
None.
References


Age–Period–Cohort Analysis of Stroke Incidence in Dijon From 1985 to 2005
Meheni Khellaf, Catherine Quantin, Philippe d'Athis, Maniane Fassa, Valérie Jooste, Marie Hervieu, Maurice Giroud and Yannick Béjot

Stroke. published online November 11, 2010;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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:
http://stroke.ahajournals.org/content/early/2010/11/11/STROKEAHA.110.592147.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/