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Background and Purpose: Temporal trends in stroke incidence in Denmark have not been previously reported. The Copenhagen City Heart Study is a prospective study based on a randomly selected sample of an urban population of, initially, 19,698 participants followed since 1976. Over a period of 12 years, we studied three important aspects of stroke incidence in 848 identified cases: temporal trends, dependence on age and sex, and comparison of responders and nonresponders.

Methods: The participants were invited to two health examinations at 5-year intervals. The participants who attended at least one of the two examinations are termed responders and those who attended none nonresponders. The cases of first-ever stroke were collected from responders, the National Patient Register, and the National Register of Deaths and were verified by study of hospital records and death certificates.

Results: For responders aged 35–64 years and ≥65 years, there were no significant changes in the weighted rates in four consecutive 3-year periods. There was a tendency toward decreasing rates among younger women, but not in older women or men. The age- and sex-adjusted rates per 1,000 (based on the Danish population in 1982) in responders in the entire 12-year follow-up period were 1.61 in women, 2.67 in men, and 2.14 in both sexes combined. Stroke incidence rates increased exponentially with age in both sexes, with rates in men generally twice those in women, even in the ≥75 years of age group. Age-adjusted rates were higher in nonresponders than in responders. For women, this ratio was 1.7; for men, 1.1.

Conclusions: The stroke incidence in Copenhagen is relatively high and has shown no decreasing tendency over the period 1976–1988.

The purpose of the present study was to analyze the incidence of initial stroke in a Danish urban population during 12 years of follow-up. This work is part of a larger prospective study, the Copenhagen City Heart Study, and is based on a randomly selected initial population sample of 19,698 participants followed since 1976. The study design, with two health examinations at 5-year intervals, permitted an analysis of three important aspects of stroke incidence: temporal trends, dependence on age and sex, and comparison of responders and nonresponders.

Subjects and Methods

The study population was chosen randomly from an area of Copenhagen served by Rigshospitalet, with approximately 90,000 inhabitants ≥20 years of age. The area contains middle- and working-class populations, and its demographic profile is representative of the Copenhagen population with <2% non-European residents. The initial sample consisted of 19,698 white Danish citizens ≥20 years of age. The study population was selected to contain mostly middle-aged persons, with fewer young and old persons. Details of the study population and sampling procedure are given elsewhere. All participants were invited by letter to an initial health examination on a specific date between March 1, 1976, and March 31, 1978, and to a second examination between April 6, 1981, and September 7, 1983. The numbers of responders to first, second, and both examinations were 14,223, 12,411, and 11,135, respectively.

The 15,499 persons who attended at least one of the two examinations will hereafter be referred to as responders. Of the initially selected sample, 371 died before the date of first examination and were excluded from the incidence analysis. Figure 1 shows the age distribution of the study population compared with the Danish population as of January 1, 1982. The two health examinations, principal source of information on responders, permitted exclusion of persons who reported cerebrovascular events before the observation period.
At the second examination, new cerebrovascular events during the first 5 years of follow-up were identified. The procedure and the complete questionnaire used at the examinations have been described. Additional information on new cerebrovascular events and events prior to the observation period was obtained through the National Health Service Register of Deaths and the National Patient Register. These registers provide unique information on all hospital admissions in Denmark, including patient and hospital unit identification, admission and discharge dates, and six-digit codes corresponding to all discharge diagnoses. However, because the National Patient Register was first established in 1976, information on previous events in nonresponders could be obtained only if they were hospitalized in the observation period and one of the discharge diagnoses referred to previous stroke.

For all the participants diagnosed with codes 430–438 of the World Health Organization's International Classification of Diseases (8th revision), hospital discharge letters were retrieved to identify those who had suffered an event. When necessary, all hospital records as well as additional information from the patient's general practitioner, family, or nursing home were collected. After the first 5 years of follow-up, we realized that no strokes could be identified in patients with codes 437 and 438; thus, in the following periods, only codes 430–436 were considered. At the second health examination, 103 stroke survivors were identified. Among these, 25 had not been hospitalized for their first stroke, and the diagnosis was based on history and neurological examination.

Death certificates were obtained from the National Health Service Register of Deaths in all cases in which stroke was registered as either underlying cause or contributing cause of death. Whenever possible, these certificates were supplied by information from other sources as stated above. In 28 cases (seven responders and 21 nonresponders; 3.3%), the diagnosis was verified on the basis of death certificates alone.

For the purpose of this study, we considered all events until December 31, 1988. Only initial stroke was considered for the incidence study, and persons with documented stroke before the initial examination were excluded. Stroke was defined as an acute disturbance of focal or global cerebral function with symptoms lasting >24 hours or leading to death. This definition excludes transient ischemic attack. Consequently, in persons who had both first-ever transient ischemic attack and first-ever stroke in the observation period, only stroke was registered as event. Persons with first transient ischemic attack before the observation period were not excluded.

Subdural, extradural, and traumatic intracranial hematoma, confirmed by cerebral computed tomographic (CT) scan, surgery, or autopsy, were not counted as events; nor was verified primary subarachnoid hemorrhage, although the above definition also refers to this event. Cerebrovascular lesions discovered at autopsy or on CT scan, without previous clinical manifestations of stroke, were not registered as stroke.

The stroke events were identified and classified after critical revision of collected information. Cases too vague to be attributed to stroke were not counted as events. The remaining events were divided into the following categories: hemispheric infarction, hemorrhagic, nonspecific hemispheric stroke, brain stem stroke, subarachnoid hemorrhage, and nonspecific stroke. All the categories except subarachnoid hemorrhage were included. The distinction between cerebral infarction and intracerebral hemorrhage was considered only in hemorrhagic strokes and required cerebral CT scan or adequate brain autopsy results. Verification of subarachnoid hemorrhage required either CT scan or autopsy or adequate clinical history and spinal fluid examination. The distinction between hemispheric and brain stem stroke was based on clinical findings unless proved otherwise by CT scan or autopsy. If such a distinction was not possible, the event was classified as nonspecific stroke.

Temporal trends in stroke incidence were studied in responders only. For each responder, the follow-up period (1976–1988) was divided into four consecutive 3-year periods. Thus, the beginning of the first period fell chronologically between March 1, 1976, and March 31, 1978. The average annual rates for each sex group and 10-year age group for a given 3-year period were calculated by dividing the number of events in the period by the number of person-years. Events and person-years referred to responders who were alive and free from stroke at the beginning of the 3-year period.

Person-years for an individual were calculated from the beginning of the 3-year period until stroke, death, or the end of the period. The ages given in the tables are average ages for the 3-year periods. Thus, for example, when the age group 45–54 years is considered in each of the four 3-year periods, it corresponds to the following age groups at the first
examination: 43.5–53.5, 40.5–50.5, 37.5–47.5, and 34.5–44.5 years, respectively.

For each period, rates for women and men, as well as for both sexes combined, were obtained by adjustment to the age and sex distribution of the Danish population in 1982. The weighted incidence rates in the age groups 35–64 and ≥65 years were obtained by adjusting to the age and sex distribution of the study population. Temporal trends were studied by linear regression analysis, and the standard $t$-test was used to determine whether the trend gradient differed significantly from zero. All probability values presented are two tailed.

The relationship between stroke and age was studied in responders by plotting average annual incidence rates for the entire 12-year follow-up period against 10-year age groups in women, men, and both sexes combined. These average rates were obtained by summing up events and person-years belonging to each group in each of the four 3-year periods.

Comparing stroke incidence in responders and nonresponders in the entire 12-year follow-up period was based on the age- and sex-adjusted rates weighted according to the age distribution of the study population at the date of the second examination.

### Results

The incidence rates for the first 5-year follow-up period, based on previously collected data, have been reported previously. These data were later supplemented with new cases, and the results for the entire follow-up period are now presented. Altogether, 848 stroke cases have been identified during the 12-year follow-up, 657 among responders and 191 among nonresponders. According to the classification criteria described earlier, these cases included 299 hemispheric infarctions, 56 hemispheric hemorrhages, 256 nonspecific hemispheric strokes, 43 brain stem strokes, and 194 nonspecific strokes. Computed tomography or autopsy was performed in 43% of the 848 cases. In addition to the 848 stroke cases, 139 cases of first transient ischemic attack and 35 cases of verified subarachnoid hemorrhage were identified (but not included in the stroke incidence analysis). Only one case of stroke was identified among participants <35 years of age. Table 1 shows the average annual sex- and age-specific incidence rates of first stroke among responders. The average annual rates per 1,000 (adjusted to the Danish population in 1982) in the 12-year follow-up period in responders were 1.61 in women, 2.67 in men, and 2.14 in both sexes combined.

The temporal trends of stroke incidence in responders are illustrated in Figure 2. There was no statistically significant change of the rates by time, although a decreasing tendency was seen in women aged 35–64 years ($p<0.1$). In each period, the weighted rates were two to three times higher in men than in women.

The age dependence of the incidence rates is depicted in Figure 3, where average annual age- and sex-specific incidence rates are presented for responders for the entire 12-year follow-up period. The stroke incidence rates increased exponentially with age, and the gradient of this log-linear dependence was similar in women and men. The corresponding rates are detailed in Table 1, which shows that rates in men were approximately twice those in women, even in the age group 75–84 years.

The average annual incidence rates were also calculated in nonresponders and were generally higher in responders. The ratio between the weighted rates in nonresponders and responders adjusted to the study population aged ≥35 years was 1.7 in women and 1.1 in men.

### Discussion

Our study fulfills most of the "ideal" criteria set up by Malmgren et al. Because the primary health...
Weighted incidence rates per 1000

3-year periods

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3-year periods

sector was not involved in the study, however, we may have missed a part of nonhospitalized strokes. Some of these cases have been identified through responders, death certificates, and later hospitalizations. It can be assumed that the ascertainment of fatal cases is complete. Among stroke survivors, some with mild stroke were not hospitalized, and some of these were missed. At the second health examination, attended by 12,411 participants, 25 persons were identified who had not been hospitalized for a first stroke. The estimated number of nonidentified strokes in the rest of the observation period is <75, corresponding to <8% of all strokes.

The incidence rates of first stroke in our study, age and sex adjusted to the Danish population in 1982, are relatively high. Rates from Shibata, Japan,7 and Söderhamn, Sweden,8 were higher, whereas rates were lower in the other "ideal" studies.8-13 The high rates in our study can be explained only partially by the high proportion of older people in the Danish population.

Age-specific incidence rates of first-ever stroke were also highest in Shibata,7 closely followed by Söderhamn (1983–1984)8 and the present study. Rates in Rochester, Minnesota;9 Tilburg, The Netherlands;10 Espoo–Kauniainen, Finland;11 Auckland, New Zealand;12 Oxfordshire, England;13 Benghazi, Libya;14 and Umbria, Italy,15 were lower.

When both age- and sex-specific rates are considered, the rates in our study were approximately two times higher in men than in women, even in the higher age groups.

Recent stroke studies from other parts of Scandinavia similarly show a twofold higher incidence in men than in women (K. Asplund, personal communication). In most earlier studies, however, the ratio between incidence rates in men and women decreases with age. Thus, for the age group 75–84 years, the male-to-female ratio in our study was 1.9 in comparison with ratios between 1 and 1.3 in other studies.8,10-13,15 Among the 103 stroke survivors identified at the second examination, the proportion of nonhospitalized cases was 38% (15 of 40) in women and 16% (10 of 63) in men. This could indicate that women with stroke in the study population were less likely to be hospitalized than men. However, it is not possible to draw definite conclusions because the 103 cases represent only 12% of the 848 strokes identified. We are at present analyzing the risk factors for stroke in the study population and will soon be able to report whether they differ from those found in other countries.

In the present study, stroke incidence showed no significant changes in time, although a tendency for decline was seen in younger women. To our knowledge, no other changes could account for the temporal trends; neither the number of medical facilities nor available physicians has increased in Copenhagen during the study period. Modern technology cannot account for the missing decline either, as the diagnosis of stroke was based on clinical criteria. Magnetic resonance imaging was not used as a diagnostic tool for stroke. The use of CT scanning increased in the last years, but in our study it served mainly to distinguish between stroke subtypes.

In no case was stroke identified on the basis of CT results alone if not preceded by relevant clinical signs. The results from Rochester showed that the decline in stroke incidence between 1945 and 1979 has stopped, and an increasing trend occurred in 1980–1984.9 In Japan, a decline of stroke incidence has been reported from two regions: Hishayama,16 between 1961 and 1976, and Ikawa,17 between 1965 and 1983. In contrast, in Söderhamn,8,18 there was a significant increase in incidence rates for women but no change for men or for the total population between 1975 and 1978 and between 1983 and 1986.
The design of the Copenhagen City Heart Study made possible the comparison of stroke incidence in responders and nonresponders. Responders constituted 79% of the study population. The ratio of stroke incidence rates, adjusted to the study population, between nonresponders and responders was 1.7 in women but only 1.1 in men. One explanation might be that stroke is a stronger selective factor in women than in men, preventing more women than men from attending the health examinations. Stroke severity and social factors, combined with the illness, might be the reason. Another explanation is that health examinations may have a stronger intervention effect in women than in men by influencing health awareness and contacts with the health sector and, thus, reducing risk factors. Part of the higher incidence rates in nonresponders might also be attributed to failure of excluding cases with nonrecognized previous stroke.

The differences between responders and nonresponders in the study population have been discussed previously. Nonresponders had a higher mortality in all age groups and in both sexes. It seems, therefore, that the higher stroke incidence in nonresponders is real.

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References


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