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Sex Differences in Incidence, Mortality, and Survival in Individuals With Stroke in Scotland, 1986 to 2005

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Background and Purpose—The aim of this study was to examine the effect of sex across different age groups and over time for stroke incidence, 30-day case-fatality, and mortality.

Methods—All first hospitalizations for stroke in Scotland (1986 to 2005) were identified using linked morbidity and mortality data. Age-specific rate ratios (RRs) for comparing women with men for both incidence and mortality were modeled with adjustment for study year and socioeconomic deprivation. Logistic regression was used to model 30-day case-fatality.

Results—Women had a lower incidence of first hospitalization than men and size of effect varied with age (55 to 64 years, RR=0.65, 95% CI 0.63 to 0.66; ≥85 years, RR=0.94, 95% CI 0.91 to 0.96). Women aged 55 to 84 years had lower mortality than men and again size of effect varied with age (65 to 74 years, RR=0.79, 95% CI 0.76 to 0.81); 75 to 84 years, RR=0.94, 95% CI 0.92 to 0.95). Conversely, women aged ≥85 years had 15% higher stroke mortality than men (RR=1.15, 95% CI 1.12 to 1.18). Adjusted risk of death within 30 days was significantly higher in women than men, and this difference increased over the 20-year period in all age groups (adjusted OR in 55 to 64 year olds 1.23, 95% CI 1.14 to 1.33 in 1986 and 1.51, 95% CI 1.39 to 1.63 in 2005).

Conclusions—We observed lower rates of incidence and mortality in younger women than men. However, higher numbers of older women in the population mean that the absolute burden of stroke is greater in women. Short-term case-fatality is greater in women of all ages and, worryingly, these differences have increased from 1986 to 2005. (*Stroke*. 2009;40:1038-1043.)

Key Words: cerebrovascular disease ■ epidemiology ■ prognosis ■ sex

Stroke is the third most common cause of death in developed countries.^{1,2} Although overall mortality from stroke is falling in western Europe and America,^{3–5} trends in incidence are less clear and there are conflicting reports of stable,⁶ increasing,^{7,8} and decreasing rates.^{5,9,10} Stroke is a disease of the elderly. As populations in developed countries age, stroke will become a major public health problem associated with significant use of healthcare resources.

It is difficult to draw clear conclusions around complex parameters such as incidence, mortality, and case-fatality and to examine the effect of age and sex within these parameters over time. There is growing literature examining sex differences in disease epidemiology, including stroke. Although there has been a positive move to present separate data for men and women, this has reduced the opportunity to explore the independent effect of sex, and few studies have examined the effect of sex across different age groups and over time. The aim of our study was to describe age-specific incidence, mortality, and 30-day case-fatality in men and women in the

entire Scottish population over a 20-year period and to examine the significance of sex within each of these parameters.

Methods

Data Sources

The National Health Service in Scotland provides primary and secondary health care, free at point of access, to all citizens. Virtually all hospitalizations for stroke are to National Health Service hospitals. The Information Services Division of National Health Service Scotland collects data on all discharges from National Health Service hospitals using the Scottish Morbidity Record Scheme. Data from patient case records are used to code up to 6, one principal and 5 secondary, diagnoses at the time of discharge according to the World Health Organization Classification of Diseases (“discharge” includes both live discharges and deaths). These data are routinely linked to information held by the General Register Office for Scotland relating to all deaths in the United Kingdom.

A first hospitalization for stroke was defined as a hospitalization with a principal diagnosis of stroke (International Classification of Diseases, 9th Revision, International Classification of Diseases 10th Revision codes: 430, 431, 433, 434, 436, I60, I61, I63, I64) with no

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previous hospitalization (principal or secondary diagnosis) for cerebrovascular disease (430 to 434, 436 to 438, I60 to I69) within 5 years. Scottish Morbidity Record Scheme identifies stroke with an accuracy of 95% when recorded in the principal diagnostic position. For the mortality analyses, a death was attributed to stroke if the primary cause of death on certification was one of the International Classification of Diseases codes cited here.

The following comorbidities were identified using principal and secondary diagnoses for any previous hospitalizations in the past 5 years and secondary diagnoses recorded in the incident stroke hospitalization: diabetes, cancer, respiratory disease, heart failure, peripheral arterial disease, atrial fibrillation, essential hypertension, renal failure, coronary heart disease, rheumatic/valvular heart disease, venous thromboembolism, depression, parkinsonism, dementia, falls and fractures, and alcohol misuse. Socioeconomic status was defined using the Carstairs-Morris index of deprivation,¹¹ an area-based measure based on postcode sector of residence.

Statistical Analyses

Annual age- and sex-specific rates of incident events for hospitalized stroke and for stroke mortality were calculated using denominator data from the 1981, 1991, and 2001 censuses with interpolation and extrapolation for the intracensus years. Rate ratios (RRs) were calculated for incidence and mortality rates to compare the ratio of women with men. These were adjusted for year of hospitalization (year of death for mortality) and socioeconomic status using Poisson regression. Fractional polynomial analysis was used to model the effect of year. We calculated 30-day case-fatality with follow-up measured from date of stroke hospitalization. There was no censored information (the cohort was followed up until December 31, 2006). Logistic regression was used to model 30-day case-fatality in men and women with adjustment for year of hospitalization, socioeconomic status, and comorbidity. Least square means were calculated to determine adjusted case-fatality at 30 days.

We determined a priori to investigate the significance of sex-by-year interactions and sex-by-age interactions. A significance level of 0.05 was used. Analyses were conducted using STATA (Version 10; STATA Corp, College Station, Texas).

Results

Patient Characteristics

Of 157 639 first hospitalizations for stroke in Scotland from 1986 to 2005, 86 913 (55%) were women. Women were on average 5 years older than men with a mean age at admission of 74 years (SD, 13.3) compared with 69 years (SD, 13.1) in men. During this period, there were 91 466 deaths due to stroke (32 854 [36%] in men). At death, like with first hospitalizations, women were on average 5 years older than men (women, 80 years [SD, 10.4]; men, 75 years [SD, 10.8]). The proportion of "stroke not specified" diagnoses fell from 76.8% in 1986 to 31.0% in 2005 in men and from 78.7% to 35.1% in women. The proportion of ischemic strokes increased (from 13.1% to 51.1% in men; 10.3% to 46.8% in women) as did intracerebral hemorrhage (5.0% to 12.4% in men; 3.9% to 10.5% in women) from 1986 to 2005. The proportion of stroke due to subarachnoid hemorrhage was invariant over time (5% in men; 7% in women).

Incidence of First Hospitalization

Age- and year-specific incidence rates were generally lower in women than men over the 20-year period (Figure A). In those age <55 years old, the incidence per 100 000 population in 1986 was 20.6 (17.5) in men (women) rising to 26.4 (22.4) in 2005. In ≥85 year olds, the incidence per 100 000 population in 1986 was 1869.5 (1606.1) in men (women)

falling to 1232.2 (1287.8) in 2005. The adjusted RRs in Table 1 show that women had statistically significantly lower incidence than men and that the size of the effect was dependent on age group (test for interaction, $P<0.0001$). The incidence for women aged between 55 to 64 years (65 to 74 years) was approximately one third (one fourth) less than men of same age groups, whereas for women aged <55 years and ≥85 years, the relative reduction was only 15% and 6%, respectively. The interaction between sex and year was statistically significant ($P=0.03$), but when this was explored by calculating the year-specific RRs, the range of values was narrow (for example, in 55 to 64 year olds group, the range was 0.64 to 0.67) and close to the average effects shown in Table 1. We have an extremely large sample size and in this case, a statistically significant result was not of practical importance.

Mortality

The age- and year-specific stroke mortality rates were mostly lower in women than men over the 20-year period apart for those aged ≥85 years in whom the reverse was seen (Figure B). In <55 year olds, the mortality rate per 100 000 in 1986 was 5.3 (6.8) in men (women) and in 2005 was 4.6 (4.1). In ≥85 year olds, the mortality rate per 100 000 in 1986 was 2260.0 (2561.4) in men (women) and in 2005 was 1143.4 (1398.1). The adjusted RRs in Table 2 show that women aged between 55 and 84 years had statistically significantly lower mortality than men in that age range. However, the size and direction of effect depended on age group (test for interaction, $P<0.0001$). For those aged ≥85 years, women had 15% higher stroke mortality than men, and for those aged <55 years, there was no statistically significant difference between the sexes. As for the incidence analyses, the interaction between sex and year was statistically significant ($P=0.01$), but again, exploration of these found them not to be of practical importance (for example, in 55 to 64 year olds, the range of RRs was 0.78 to 0.84 compared with 0.80 when ignoring interaction; Table 2).

Case-Fatality

The observed age- and year-specific 30-day case-fatality estimates were in general higher in women than men over the 20-year period (Figure C). In those <55 years old, case-fatality in 1986 was 22.7% (28.4%) in men (women) falling to 11.7% (12.7%) in 2005. In ≥85 year olds, case-fatality in 1986 was 41.0% (37.3%) in men (women) falling to 32.0% (31.8%) in men (women) in 2005. The adjusted ORs in Table 3 show that women had higher odds of death within 30 days of first hospitalization of stroke than men, and the size of effect depended on age group (test for interaction, $P<0.0001$). The effect was largest in those aged 55 to 64 years and smallest in those ≥85 years old. The interaction between sex and year was statistically significant ($P<0.0001$) and the difference in ORs across the years was considerable. In Table 3, the adjusted ORs in 2005 are greater than the corresponding ORs in 1986 indicating that the relative difference between the sexes in 30-day case-fatality has widened over the 20-year period. The difference between men and women in adjusted case-fatality increased between 1986 and 2005 in all age groups.

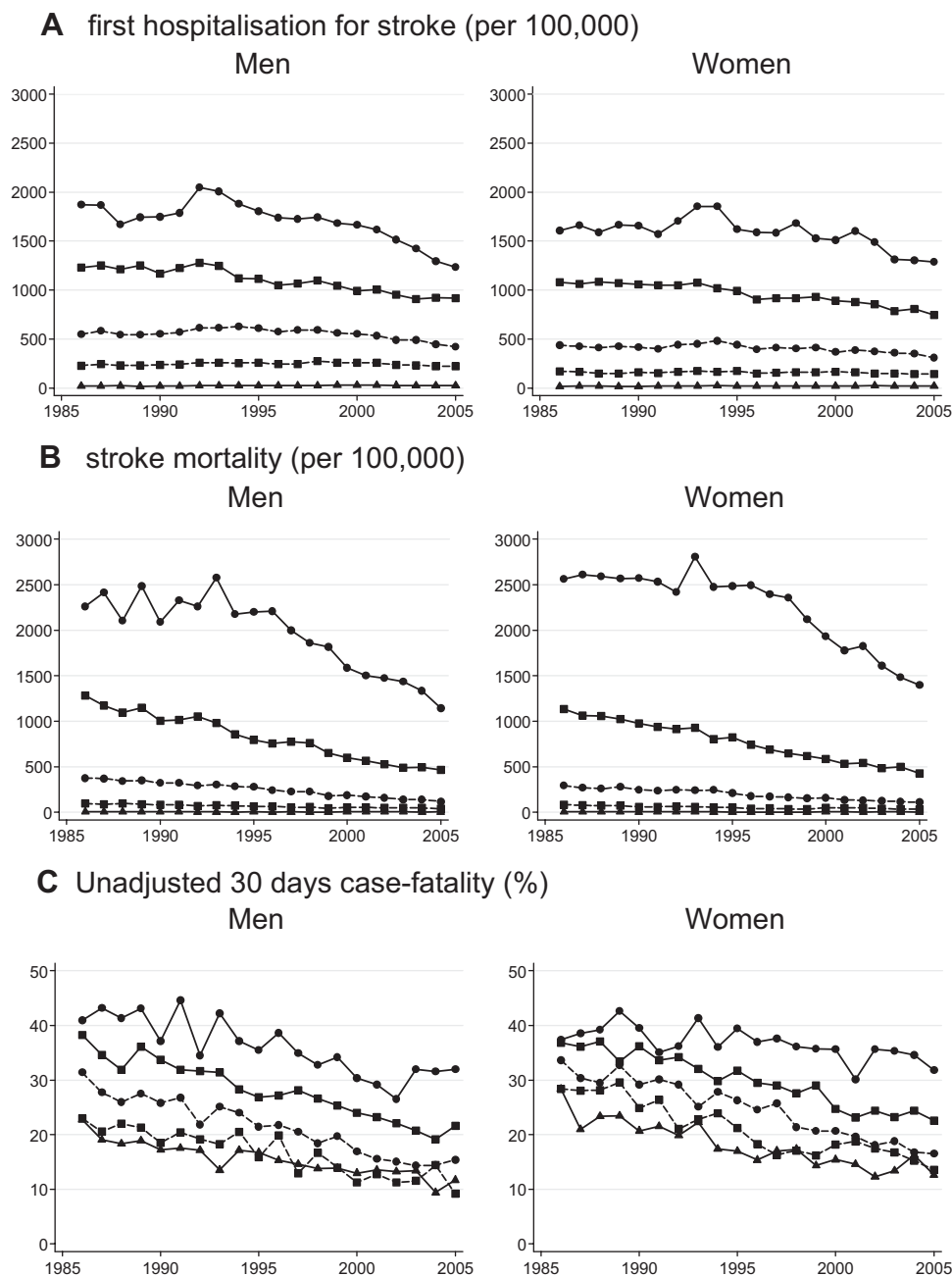


Figure. Age and sex specific rates (per 100 000) of (A) first hospitalization for stroke; (B) stroke mortality; and (C) unadjusted 30-day case-fatality (%). <55 years, solid line, triangles; 55 to 64 years, dashed line, squares; 65 to 74 years, dashed line, circles; 75 to 84 years, solid line, squares; ≥85 years, solid line, circles.

Discussion

This is one of the largest population-based studies to examine trends in incidence and 30-day case-fatality after hospitalization with an incident stroke as well as population mortality from stroke in men and women. We examined incidence and 30-day case-fatality in 157 639 individuals with a first stroke hospitalization in Scotland over 2 decades. We also examined population mortality rates attributed to stroke in 91 466 individuals over the same time period.

Incidence

We found that women had a lower incidence of stroke than men in all age groups, although the female-to-male RR varied

according to age. The greatest disparity was in those aged 55 to 64 and 65 to 74 years in whom the RR was 0.65 and 0.73, respectively. This difference was still present, although less evident, in the young and very elderly. Although incidence declined over the study period, the effect of sex did not change substantially with the male-to-female RR remaining relatively stable over time. Few studies have described temporal trends in sex- and age-specific incidence rates, many reporting adjusted rates or absolute numbers.^{5,9} The findings from this study are consistent with those reported by a small number of similar population-based studies. A study of hospitalization and death data in the Minneapolis–St Paul area examined stroke hospitalization rates in 2000 to 2002

Table 1. RRs of Incidence of First Hospitalization for Stroke for Women Compared With Men

Age Group, years	RRs* Women Versus Men (95% CI)
<55	0.85 (0.82–0.88)
55–64	0.65 (0.63–0.66)
65–74	0.73 (0.72–0.75)
75–84	0.87 (0.85–0.88)
≥85	0.94 (0.91–0.96)

*Adjusted for year of admission and socioeconomic deprivation.

and reported higher hospitalization rates in men than in women for each age group with a greater disparity in those aged 50 to 69 and 70 to 79 years (RRs 0.76 and 0.73, respectively) than in the young and very elderly.¹² In the National Hospital Discharge Survey, stroke hospitalization rates were greater in men than in women up to the age of 74 years with no sex difference thereafter.⁵ A study of the Swedish Hospital Discharge Register examining stroke hospitalizations in those age 30 to 65 years reported a male excess in stroke incidence rates with a male to female RR of 0.49 in 1989 to 1991, which decreased over time to 0.55 in 1998 to 2000.⁷ In contrast to this study, stroke incidence increased over the time period, more so in women than in men. It is clear that men are at higher risk of experiencing a stroke hospitalization and that this excess male risk is seen across all age groups. The commonly suggested explanation for the reduced risk seen in women is related to sex steroid hormones, although studies of exogenous hormone therapy have had negative findings.^{13,14} Interestingly, although stroke incidence has declined, the male-to-female RR has remained relatively stable over time for each age group suggesting that primary preventative measures have been equally effective in men and women. This is a new finding and there are no other data with which to compare these findings.

Mortality

Similar to stroke incidence rates, population stroke mortality rates were lower in women than in men except in those aged ≥85 years old in whom there was an excess risk of 15% in women. The findings from this study are consistent with the few studies that have described age- and sex-specific mortality rates.^{3,12} The Minneapolis–St Paul Study reported population mortality rates for men and women in 2000 to 2002.¹²

Table 2. RRs of Stroke Mortality for Women Compared With Men

Age Group, years	RRs* Women Versus Men (95% CI)
<55	0.96 (0.90–1.03)
55–64	0.80 (0.77–0.84)
65–74	0.79 (0.76–0.81)
75–84	0.94 (0.92–0.95)
≥85	1.15 (1.12–1.18)

*Adjusted for year of study and socioeconomic deprivation.

Rates were greater in men than women in those aged <80 years but thereafter were greater in women than men with a female to male RR of 1.06. The Oxford Record Linkage Study also reported a 14% excess in stroke mortality in women aged ≥85 years.³ Although an interaction for year and sex was significant, differences were small and the female-to-male RR remained relatively stable over the study period. These findings have not been reported previously but are in keeping with the results of the Oxford Linkage Study.³

Case-Fatality

We found that adjusted case-fatality at 30 days was greater in women than in men, although the size of the effect depended on age; women aged 55 to 64 years were at a 35% increased risk of death after adjusting for other factors. Previous studies of short-term case-fatality after incident stroke have reported conflicting findings with evidence of increased risk in women,^{15,16} decreased risk,^{6,17} and no sex difference.¹⁸ This is the first study to examine the interaction between sex and age in short-term case-fatality over time after an incident stroke. In our study, there was a highly significant interaction between sex and year with evidence of a widening difference in 30-day case-fatality between men and women. Although we have not reported trends in adjusted 30-day case-fatality for the purposes of this study, unadjusted analyses would suggest that this is due to a greater decline in case-fatality in men than in women over the study period. This is a new and interesting finding. The Quebec Study reported similar declines in unadjusted case-fatality in men and women between 1988 and 2002⁹ as did the National Hospital Discharge Survey, which examined in-hospital case-fatality in men and women between 1988 and 1997⁵ and the Minneapolis–St Paul Study.^{5,9,12} It is not clear why declines in 30-day case-fatality

Table 3. ORs and Adjusted 30-Day Case-Fatality for Women Compared With Men

Age Group, years	Overall	1986†	2005†	Adjusted‡ 30-Day Case-Fatality, %			
	ORs* Women Versus Men (95% CI)	ORs* Women Versus Men (95% CI)	ORs* Women Versus Men (95% CI)	1986 Women (95% CI)	1986 Men (95% CI)	2005 Women (95% CI)	2005 Men (95% CI)
<55	1.19 (1.10–1.30)	1.08 (0.99–1.19)	1.33 (1.21–1.46)	27.1 (22.0–32.9)	25.6 (20.7–31.2)	17.3 (13.7–21.6)	13.6 (10.7–17.2)
55–64	1.35 (1.26–1.44)	1.23 (1.14–1.33)	1.51 (1.39–1.63)	31.6 (26.0–37.8)	27.3 (22.2–33.0)	20.6 (16.5–25.4)	14.7 (11.6–18.4)
65–74	1.25 (1.19–1.31)	1.14 (1.08–1.21)	1.40 (1.31–1.49)	36.4 (30.4–42.9)	33.4 (27.7–39.7)	24.3 (19.7–29.6)	18.7 (15.0–23.1)
75–84	1.14 (1.09–1.18)	1.04 (0.98–1.09)	1.27 (1.20–1.35)	42.0 (35.6–48.7)	41.1 (34.8–47.8)	28.9 (23.7–34.7)	24.3 (19.7–29.5)
85+	1.09 (1.02–1.16)	0.98 (0.91–1.06)	1.20 (1.12–1.29)	49.1 (42.4–55.9)	49.5 (42.7–56.4)	35.2 (29.3–41.5)	31.1 (25.6–37.1)

*Adjusted for year of admission, socioeconomic deprivation, and comorbidity.

†ORs for 1986 and 2005 when accounting for year-by-sex interaction ($P<0.0001$).

‡Least square means from model that includes year-by-sex interaction and adjusted for comorbidities and socioeconomic deprivation.

should be greater in men than in women, whereas falls in incidence and mortality are similar. One possibility is that women are less likely than men to receive care on an acute stroke unit.¹⁹ A number of studies have shown that women hospitalized after a stroke undergo fewer diagnostic procedures than men^{15,20} and are less likely to receive thrombolytic treatment^{20,21}; however, these factors could not explain our findings. In addition, there is evidence of an increased admission threshold in women, especially elderly women.²¹ Increased stroke severity in women compared with men could partly explain our findings, although the evidence for this is not consistent^{15,19,22} and may be further complicated by changing admission thresholds in both men and women over time.^{23,24} These differences may also be influenced by differing rates of admission to hospital in men and women. However, a meta-analysis of community-based studies of ischemic stroke reported no difference in the proportion of patients managed in the hospital versus the community according to sex.²⁵ We did not find any evidence that stroke subtype had differentially changed according to sex over the study period. This is unlikely therefore to explain our findings. The explanation for increased short-term case-fatality in women compared with men is likely to be multifactorial and requires further investigation, especially because this disparity has increased over time.

Strengths and Limitations

We have used routinely available linked hospital discharge data to examine the effect of sex on incidence, mortality, and 30-day case-fatality for stroke in an entire population over a 20-year time period. The size of this study has enabled us to examine the effect of sex by age and over time, which has not been previously possible.

This study has a number of limitations. Mortality data based on underlying cause alone are likely to underestimate mortality and the associated burden of disease.³ Furthermore, hospital discharge data will only identify patients admitted to the hospital with stroke. Several registry-based studies report that >90% of patients with stroke are managed in the hospital,^{8,26} a figure that is similar in Scotland.²⁷ Several registry-based studies have reported a reduction in stroke severity over time^{23,28} and hospitalization of milder strokes may distort trends in case-fatality. We do not have information on stroke severity. However, the evidence for an effect on differences in case-fatality between men and women is not consistent.^{15,19,22} We have not examined the effect of sex by stroke subtype and there is limited evidence to suggest that female-to-male mortality varies according to subtype.²⁹ Stroke subtype was not reliably recorded in the early years of this data set and remains "unspecified" in approximately one third of incident hospitalizations for stroke in Scotland in 2005.

Summary

In conclusion, we have examined sex differences by age and over time for stroke incidence, 30-day case-fatality, and population mortality for a population of 5.1 million. We have found that the incidence of stroke is greater in

men than in women of all ages, that population mortality rates are greater in men than women up to the age of 84 years, and that there have been similar declines in both incidence and mortality in men and women over a 20-year period. The excess of older women means that the absolute burden in terms of absolute numbers of stroke is greater in women than in men. Short-term case-fatality is greater in women than men of all ages and, worryingly, these differences have increased over time.

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Disclosures

None.

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