Recent Patterns of Sex-Specific Midlife Stroke Hospitalization Rates in the United States

Amytis Towfighi, MD; Daniela Markovic, MS; Bruce Ovbiagele, MD, MS

Background and Purpose—Little is known about sex-specific stroke hospitalization rates among middle-aged individuals. This study assessed recent temporal trends in stroke hospitalizations among persons aged 35 to 64 years in the United States.

Methods—The Nationwide Inpatient Sample was used to identify individuals with a primary or secondary discharge diagnosis of stroke between 1997 and 2006 (n=3,161,752). Age-adjusted sex-specific rates of ischemic and hemorrhagic stroke hospitalizations were assessed among individuals aged 35 to 64 years.

Results—Over the study period, stroke hospitalization rates per 100 000 decreased by 10% from 66.7 to 60.3 (trend P<0.01) in men and 8% from 52.7 to 48.3 (trend P<0.001) in women. The 55- to 64-year age group drove reductions in hospitalization rates: slope (rate of change per year) = −12.3 for men and −8.9 for women (both P<0.001). Rates increased slightly in men and women aged 35 to 44 years and remained stable for persons aged 45 to 54 years. Stroke subtype analysis revealed that rates of ischemic stroke hospitalization increased and hemorrhagic stroke hospitalization remained stable among individuals aged 35 to 44 years. Rates of ischemic and hemorrhagic stroke hospitalizations remained stable among those aged 45 to 54 years and decreased among persons aged 55 to 64 years.

Conclusions—From 1997 to 2006, ischemic and hemorrhagic stroke hospitalization rates declined among individuals aged 55 to 64 years and remained stable among persons aged 45 to 54 years; ischemic stroke hospitalization rates increased among individuals aged 35 to 44 years. Further studies are needed to assess and address increases in ischemic stroke hospitalizations among younger individuals. (Stroke. 2011;42:3029-3033.)

Key Words: acute stroke ■ gender ■ hospitalization ■ middle-aged ■ midlife ■ sex-specific disparities ■ trends ■ United States

The overwhelming majority of strokes occur in persons aged ≥65 years1; therefore, data on stroke occurrence among relatively younger individuals, especially those in their midlife years (35 to 64 years), are rather scarce. Furthermore, information on the potential influences of sex on stroke in this latter demographic are limited2 despite the unique stroke risk factors harbored by women <65 years, including pregnancy, oral contraceptive use, higher prevalence of migraines, and use of hormone replacement therapy.3

Recent nationwide stroke prevalence data obtained through self-report in the United States indicate that stroke rates among middle-aged men have remained stable in recent years, whereas that of similarly aged women have increased. Indeed, women aged 35 to 54 years who participated in cross-sectional nationwide surveys from 1999 to 2004 were 3 times more likely to have experienced a stroke compared with similarly aged women surveyed in 1988 to 1994 (1.8% versus 0.6%, P=0.003), but stroke prevalence among men did not change (0.9% versus 1.0%, nonsignificant).4 It is unclear if this apparent increase in stroke prevalence among middle-aged women was due to an increase in stroke incidence or improved stroke survival among younger/middle-aged women.

Available data suggest that among individuals <45 years, there are no sex differences in stroke mortality; however, among those aged 45 to 74 years, women have lower stroke mortality rates than men.2,5 Although studies have consistently shown lower stroke incidence among women aged 55 to 64 years compared with men,6-8 only 1 study has explored sex differences in age-specific stroke incidence among individuals aged <55 years and found that women had higher stroke incidence than men before age 34 years, but men had higher stroke incidence than women from 35 to 54 years of age6; the higher incidence of stroke among women <35 years of age is likely driven by higher rates of subarachnoid hemorrhage.
To address this knowledge gap, the aim of this study was to assess temporal trends from 1997 to 2006 in age-specific ischemic and hemorrhagic stroke hospitalization rates in men and women aged 35 to 64 years. Stroke hospitalization rates were used as a proxy for stroke incidence.

Methods

Population for Study
Data were obtained from the Nationwide Inpatient Sample (NIS), developed as part of the Healthcare Cost and Utilization Project, a Federal–state–industry partnership sponsored by the Agency for Healthcare Research and Quality. NIS is designed to approximate a stratified 20% sample of all non-Federal, short-term, general, and specialty hospitals serving adults in the United States. The sampling strategy selects hospitals within states that have state inpatient databases according to defined strata based on ownership, bed size, teaching status, urban/rural location, and region. All discharges from sampled hospitals for the calendar year are then selected for inclusion into NIS. To allow extrapolation for national estimates, both hospital and discharge weights are provided. Detailed information on the design of the NIS is available at www.hcup-us.ahrq.gov. From 1997 to 2006, NIS captured discharge-level information on primary and secondary diagnoses and procedures, discharge vital status, and demographics on several million discharges per year. Data elements that could directly or indirectly identify individuals are excluded. The unit of analysis was the discharge rather than the individual; discharges were therefore all considered independent. A unique hospital identifier allows for linkage of discharge data to an NIS data set with hospital characteristics.

All patients with a primary or secondary discharge diagnosis of stroke (International Classification of Diseases, 9th Revision, Clinical Modification procedure codes 430.xx to 438.xx) aged 35 to 64 years at the time of hospital admission were included regardless of whether they were alive or dead at the time of discharge. Using primary and all secondary International Classification of Diseases, 9th Revision, Clinical Modification codes 430 to 438 provides virtually complete ascertainment of the occurrence of strokes admitted to the hospital but overestimates the number of hospitalized strokes in the population by a factor of 2.9 Assessing only primary discharge codes lowers the false-positive rate but decreases the ascertainment of stroke from 97% to 84%, and there are few data showing the sensitivity and specificity of this strategy.10–12 Furthermore, an analysis using only primary discharge codes would also be complicated by having to compute the proportion of hospital-based strokes not identified (ie, false-negative rate). By assuming that using both primary and secondary codes identified all hospital strokes (ie, a false-negative rate of 0), Williams and colleagues accounted for any potential overascertainment of this approach by making an appropriate correction in the analysis for each code.13 By this procedure, the estimated number of strokes by International Classification of Diseases, 9th Revision, Clinical Modification code 430 to 438 was obtained by multiplying the number of discharges with each International Classification of Diseases, 9th Revision, Clinical Modification code by its estimated positive predicted value for stroke.13 The positive predicted values were derived by Williams et al by pooling data from 4 studies.13 The total number of stroke hospitalizations was obtained by summing across codes. For patients who had ≥1 reported code 430 to 438, only the first reported code was included in the analysis.

Demographic Data and Hospital Factors
The following factors were assessed: sex, race/ethnicity (white, black, Hispanic, other), primary payer (Medicare, Medicaid, private, other), hospital region (northeast, midwest, south, west), hospital location (urban, rural), admission source (emergency department, another health facility, routine), age, and length of stay.

Comorbid Conditions
The presence of the following comorbid conditions was assessed among hospitalized persons that were coded in the NIS: hypertension, diabetes with and without complications, atrial fibrillation, myocardial infarction, congestive heart failure, and peripheral vascular disease.

Statistical Analyses
We computed the weighted frequencies of stroke hospitalizations by year, sex, stroke subtype, and age group using Healthcare Cost and Utilization Project–NIS data to obtain the rate numerators. Rate denominators were obtained using US census data. Age standardization was subsequently performed using the 2000 standard US population. Race was not adjusted for given the large amount of missing data on this variable (25%). We tested for significant trends in hospitalization rates using linear regression. To test for curvilinear trends, we included year as a continuous variable together with the quadratic term to the regression models. The probability values for assessing sex differences in hospitalization rates across the 10-year study period were computed using Z-tests. All data analyses were conducted using SAS (Version 9.1; SAS Institute Inc, Cary, NC). Statistical hypotheses were tested using P<0.05 as the level of statistical significance.

We carried out trend analyses for comparing length of stay and comorbid conditions across time by age and sex using linear and logistic regression after adjusting for the survey design. The variable for length of stay was log transformed before the analysis to improve normality.

Results
By comparing individuals in 1997 and 2006, we found that the populations were similar with respect to sex, race, primary payer, hospital region, hospital location, admission source, and age. In both years, the predominant race was white (64.5% and 59.6%), most stroke admissions were in urban hospitals (87.1% and 90.3%), and most patients were admitted through emergency departments (61.7% and 69.3%). However, the proportion of patients encountered at teaching hospitals rose by approximately 14 percentage points by 2006 (from 40.5% to 55.0%). Trend analysis indicated length of stay decreased across time regardless of age or sex.

Temporal trends in vascular risk factors revealed that prevalence of congestive heart failure, peripheral vascular disease, diabetes without complications, and hypertension among hospitalized patients increased across time regardless of age or sex. The prevalence of myocardial infarction also increased across time, although the results were not significant for men aged <55 years. The prevalence of atrial fibrillation increased across time for men of all ages and women aged ≥54 years but did not change for women <55 years. Diabetes with complications was the only factor that decreased across time, but the decrease was only statistically significant for women aged ≥44 years.

Analysis of sex-specific stroke hospitalization rates from 1997 to 2006 revealed that rates were consistently higher in men aged 35 to 64 years compared with similarly aged women across the entire study period (Figure 1). Stroke hospitalization rates slightly decreased in both sexes across the study period; the age-standardized stroke hospitalization rate decreased by 10% from 66.7 to 60.3 stroke hospitalizations per 100 000 persons (curvilinear trend: P<0.01) from 1997 to 2006 in men and by 8% from 52.7 to 48.3 stroke hospitalizations per 100 000 persons (linear trend: P<0.001) in women.
Figure 2 shows the age-specific stroke hospitalization rates for successive midlife decades in men and women. Also shown are the corresponding slopes (rates of change per year) and probability values for slope comparisons between sexes and across age groups (Table). Overall, the results indicate that the 55- to 64-year age group was the only group that showed reductions in stroke hospitalizations for both men (slope = −12.3; P < 0.001) and women (slope = −8.9; P < 0.001; Figure 2C). For the 45- to 54-year age group, stroke hospitalization rates did not change (Figure 2B), whereas for the 35- to 44-year age group, stroke hospitalization rates slightly increased in both men (slope = 0.71; P = 0.008) and women (slope = 0.89, P < 0.001; Figure 2A). The increase was slightly more pronounced in women; however, the CIs overlapped.

The rate of change per year in stroke hospitalization rates did not differ between men and women aged 35 to 44 years.
Discussion

From 1997 to 2006, age-adjusted stroke hospitalization rates decreased among both men and women aged 35 to 64 years in the United States. The decrease was driven by the 55- to 64-year age group; among those aged 45 to 54 years, stroke hospitalization rates did not change and among those aged 35 to 44 years, stroke hospitalization rates actually increased. In addition, men consistently had higher stroke hospitalization rates than women in the 45- to 64- (but not in the 35- to 44-) year age group.

Analysis of trends by stroke subtype revealed that ischemic stroke hospitalization rates have increased among individuals aged 35 to 44 years, stayed stable among persons aged 45 to 54 years, and have decreased among individuals aged 55 to 64 years. Hemorrhagic stroke hospitalization rates, on the other hand, have not changed appreciably among individuals aged 35 to 54 years but have decreased among those aged 55 to 64 years. Ischemic stroke was more common in men compared with women aged 45 to 64 years and hemorrhagic stroke was more common in men compared with women aged 55 to 64 years.

The reduction in stroke admissions among individuals aged 35 to 64 years is consistent with reports of overall declines in stroke hospitalizations among adults in the United States. The decline may be due to improved risk factor control. Although our study showed an increase in rates of vascular risk factors such as hypertension and diabetes, several lines of evidence show improvements in risk factor control among individuals in the United States. Data from cross-sectional samples of the US adult population reveal that from 1988 to 1994 to 1999 to 2004, blood pressure treatment rates improved from 53.1% to 61.4%, blood pressure control rates improved from 26.1% to 35.1%, the use of lipid-lowering medications has increased from 11.7% to 40.8%, and low-density lipoprotein control improved from 4.0% to 25.1% (all \(P=0.001\)). In addition, smoking rates have declined from 29.3% in 1988 to 1994 to 26.4% in 1999 to 2000. Several studies have specifically assessed temporal trends in vascular risk factors among middle-aged individuals, but 1 study found that among men aged 35 to 54 years, systolic blood pressure decreased from 124.2 to 121.9 mm Hg and history of smoking decreased from 68.5% to 56.8% from 1988 to 1994 to 1999 to 2004; on the other hand, blood pressure and smoking rates remained stable among similarly aged women.

The reassuring reduction in overall stroke hospitalization rates among those aged 35 to 64 years is tempered by the increase in stroke hospitalization rates among the 35- to 44-year subset and lack of improvement in the 45- to 54-year subset. A study of incidence of fatal and nonfatal hospitalized stroke in Scotland from 1986 to 2005 yielded similar findings: among both men and women aged <55 years, the overall incidence rate of stroke was significantly higher in 2005 than in 1986. The slight (although insignificant) trend toward a more pronounced increase among women compared with men aged 35 to 44 years is intriguing in light of recent findings of higher stroke prevalence rates among women aged 45 to 54 years in the United States and suggests that a disproportionate increase in incidence among younger women compared with men is contributing to the emerging midlife sex disparity in stroke prevalence. Further studies of sex-specific stroke incidence and mortality among young and middle-aged individuals will help us to gain a better understanding of these findings.

The findings of higher stroke hospitalization rates among men compared with women aged 45 to 64 years in this study are consistent with several population-based studies of stroke incidence. The Greater Cincinnati–Northern Kentucky Stroke Study (GCNKSS) showed that stroke incidence among women aged 45 to 74 years was lower compared with men. A population-based study in Sweden found that women aged 55 to 64 years had a 60% lower stroke incidence than similarly aged men, but by the age of 75 years, women had a

### Table. Slope (Rate of Change per Year) for Stroke Hospitalizations in the United States From 1997 to 2006 Among Men and Women at Midlife

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age Range</th>
<th>Estimated Slope</th>
<th>SE</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>35 to 44 y</td>
<td>0.71</td>
<td>0.19</td>
<td>0.33</td>
<td>1.08</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>45 to 54 y</td>
<td>0.72</td>
<td>0.81</td>
<td>−0.87</td>
<td>2.30</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>55 to 64 y</td>
<td>−12.27</td>
<td>0.78</td>
<td>−13.80</td>
<td>−10.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>35 to 44 y</td>
<td>0.89</td>
<td>0.16</td>
<td>0.57</td>
<td>1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>45 to 54 y</td>
<td>0.05</td>
<td>0.31</td>
<td>−0.55</td>
<td>0.66</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>55 to 64 y</td>
<td>−8.88</td>
<td>0.76</td>
<td>−10.36</td>
<td>−7.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(\text{CL indicates confidence limit; SE, standard error.}\)
50% higher stroke incidence than men. The Oxford Vascular Study showed that women had lower stroke incidence than men aged 55 to 74 years, but among those aged >85 years, women had a higher stroke incidence than men.

This is the first study that we are aware of to assess temporal trends in sex- and age-specific stroke hospitalization rates in the United States. The study was strengthened by its nationwide scope, age standardization, hospital-diagnosed strokes, differentiation between ischemic and hemorrhagic strokes, and particularly by its inclusion of both primary and secondary diagnoses (which minimized the false-negative rate) with simultaneous correction for any potential overascertainment (which minimized the false-positive rate). It was limited, however, by an inability to distinguish first from recurrent strokes, lack of information regarding pregnancy-associated stroke, potential double-counting of individuals, possible inaccurate physician and administrative reporting of International Classification of Diseases codes, and lack of documented information on the rate of nonhospitalized stroke in the country.

Disclosures

None.

References

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Supplemental Figure 1

The graph shows the ischemic stroke hospitalization rate per 100,000 persons aged 35-44 years from 1997 to 2006. The rates are depicted separately for men (black line) and women (gray line). The rates show a general trend of increase over the years.
Supplemental Figure 3

Ischemic stroke hospitalization rate per 100,000 persons aged 45-54 years

Year


Men

Women
Supplemental Figure 5

Ischemic stroke hospitalization rate per 100,000 persons aged 55-64 years

Year


Men
Women
Supplemental Figure 6

The graph shows the trend in hemorrhagic stroke hospitalization rate per 100,000 persons aged 55-64 years from 1997 to 2006. The data is separated by gender, with black lines representing men and gray lines representing women. There is a noticeable decrease in hospitalization rates over the years for both genders, with women showing a slightly higher rate compared to men in most years. Error bars indicate the variability or uncertainty in the data.
Supplemental Figure Legend

**Supplemental Figure 1.** Ischemic stroke hospitalization rates for men and women aged 35-44 years from 1997 to 2006

**Supplemental Figure 2.** Hemorrhagic stroke hospitalization rates for men and women aged 35-44 years from 1997 to 2006

**Supplemental Figure 3.** Ischemic stroke hospitalization rates for men and women aged 44-54 years from 1997 to 2006

**Supplemental Figure 4.** Hemorrhagic stroke hospitalization rates for men and women aged 44-54 years from 1997 to 2006

**Supplemental Figure 5.** Ischemic stroke hospitalization rates for men and women aged 55-64 years from 1997 to 2006

**Supplemental Figure 6.** Hemorrhagic stroke hospitalization rates for men and women aged 55-64 years from 1997 to 2006