Sex Differences in Trends of Incidence and Mortality of First-Ever Stroke in Rural Tianjin, China, From 1992 to 2012

Jinghua Wang, PhD; Xianjia Ning, PhD*; Li Yang, MD; Jun Tu, BS; Hongfei Gu, MD; Changqing Zhan, BS; Wenjuan Zhang, MD; Ta-Chen Su, MD, PhD*

Background and Purpose—Sex differences in secular trends of stroke incidence are rarely reported. We aimed to explore sex differences in incidence and mortality of stroke in rural China from 1992 to 2012.

Methods—In 1992, 14,920 residents were recruited to participate in the Tianjin Brain Study, a population-based study on stroke surveillance. Stroke events and all deaths were annually registered.

Results—We observed 908 incident strokes (366 in women) from 1992 to 2012. Women were significantly younger than men (64±12 versus 68±11 years) in 1992 to 1998 (P=0.024). The incidence of first-ever stroke per 100,000 person-years for men was 166 in 1992 to 1998, 227 in 1999 to 2005, and 376 in 2006 to 2012; for women, the rates were 86 (1992–1998), 148 (1999–2005), and 264 (2006–2012). From 1992 to 2012, the incidence grew annually by 5.8% in men and 8.0% in women. The male/female incidence ratio declined significantly: 1.9 in 1992 to 1998, 1.5 in 1999 to 2005, and 1.4 in 2006 to 2012. There were no significant sex differences in mortality. The prevalence of obesity and diabetes mellitus, the levels of total cholesterol and triglycerides, and the age of menopause and reproductive years in women concurrently increased in 2011.

Conclusions—There was a significant increase in the incidence of first-ever stroke in women annually and a declining trend in the male/female rate ratio in rural China during the past 21 years. These results suggest that stroke will become one of the major diseases affecting women in future decades in China. (Stroke. 2014;45:1626-1631.)

Key Words: China ◼ risk factors ◼ surveillance

Stroke has a greater effect on women than on men.1–3 Although age-specific stroke incidence and mortality are higher in men, the number of strokes is higher and the outcomes are worse in women because the incidence of stroke is greater in older age groups and women have longer longevity.4,5 Worldwide, stroke incidence is 33% higher and stroke prevalence is 41% higher in men than in women.6

Statistics from 2010 indicate that stroke is the leading cause of death in China’s rural areas and the third leading cause of death in urban areas. More than half of the Chinese population live in rural areas, and they tend to have poor medical insurance, low educational level, and low income.7 Therefore, the prevention of stroke in rural China is crucial.

The epidemiological transition of stroke incidence and mortality has previously been studied within both the urban and rural populations in China.8–10 However, sex differences in stroke incidence and mortality remain unclear; in particular, there are no studies assessing sex differences in secular trends of stroke incidence and mortality of first-ever stroke among rural residents.

We explored sex differences in incidence and mortality and secular trends of first-ever stroke by age and concurrent changes in cardiovascular risk factors from 1992 to 2012 in Tianjin, China.

Study Population

The study population was recruited to the Tianjin Brain Study (TBS), a population-based study on stroke surveillance and all deaths were annually registered. Stroke events and all deaths were annually registered.

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and 40% in women for residents aged 35 to 74 years in 1991.11 Few residents were covered by national medical insurance before 2008.12 The residents used to live in the same village for generations based on the household registration system and traditional habit, except married daughters or those going to the universities. Ten percent of men aged 35 to 64 years usually go to cities for seasonal work and go back home for harvests and festivities at least four times a year. The events and death because of stroke have been monitored in this population since 1985. In this study, we analyzed the events and death because of first-ever stroke from 1992, because there was no imaged diagnosis technique before 1992 in this area.

The population size by 5-year age strata for men and women was obtained from the local Permanent Resident Registry. The population was adjusted by adding births and migrants as well as deducting deaths and emigrants from January 1 through December 31 of each year. The ethics committee of Tianjin Medical University General Hospital approved the study, and informed consent for each resident was obtained during recruitment.

Definition and Registration of Stroke
A first-ever stroke event was defined as the first occurrence of rapidly developing signs of focal neurological disturbance with a presumed vascular cause lasting ≥24 hours.13 Transient ischemic attacks and silent strokes (diagnosed by imaging without clinical symptoms and signs) were excluded. During the early phase of this study (1992–1998), the diagnosis of stroke events among patients with no imaging data was confirmed on clinical examinations of nonhospitalized patients and medical records of hospitalized patients.

Ascertaining Stroke Events and Death
Information on stroke events was obtained from 3 sources: local licensed village doctors reporting according to a predetermined procedure, medical records for hospital inpatients, and the All Causes of Death Registry. Local licensed village doctors reported stroke events to the community hospital <24 hours of onset. For outpatients, doctors of the community hospital visited the patients at home to confirm stroke events <72 hours of stroke onset. They then reported all events to Tianjin Medical University General Hospital. Finally, all reported stroke events were verified biannually through a door-to-door survey by senior neurologists at Tianjin Medical University General Hospital. To ensure accurate recording of stroke events, the Quality Control Group, which consisted of senior epidemiologists and neurologists from the Department of Neurology at Tianjin Medical University General Hospital, trained local licensed village doctors and doctors of community hospitals on the study protocol and conducted a survey annually using multiple overlapping sources, including the hospital admissions registry, the local death register, and interviews with patient’s relatives, in an effort to track down any unreported events. Death from first-ever stroke was defined as death occurring <30 days of stroke onset.

Cardiovascular Risk Factors Survey
The cardiovascular risk factors were examined in 1991 and 2011. The method of population sampling has been published.11 Briefly, 2196 (73%) participants in 1991 and 1939 (78%) participants in 2011, aged 35 to 74 years without previous history of coronary heart disease or stroke, were involved in the survey.11 The surveys were conducted through face-to-face interviews and performed by trained research staff and guided by epidemiological professionals. Data were collected with regard to name, sex, date of birth, and educational level; previous history of hypertension, diabetes mellitus, coronary heart disease, and stroke; and cigarette smoking (≥1 cigarette per day for ≥1 year) and alcohol use (drinking alcohol at least 1 time per week for 1 year). Physical examinations included measurement of blood pressure (BP), height, and weight. Body mass index was calculated as weight (kg) divided by the square of height (m²); obesity was defined as body mass index ≥28 kg/m². BP measurements were described in a previous study and recorded as the mean of 2 measurements taken 5 minutes apart after resting in the sitting position. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or receiving medication for hypertension. Fasting glucose, total cholesterol, and triglycerides in serum were analyzed in the central laboratory of the Tianjin Neurological Institute in 1991 and 2011. Because of limited funding, we were only able to test serum levels of fasting glucose, total cholesterol, and triglycerides in 1092 participants in 35- to 64-year age group in 1991. Reproductive years were calculated by subtracting the age of menarche (years) from the age of menopause (years).

Statistical Analysis
Because computed tomography has been widely used since 1999 and MRI became available in 2006, stroke incidence and mortality were analyzed in 3 separate periods, 1992 to 1998, 1999 to 2005, and 2006 to 2012, in both men and women by 6 age groups: <35, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and ≥75 years. The age-standardized incidences and mortality were calculated with the direct method using the world standard population by 10 age groups: <35, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and ≥75 years.14 Differences between men and women in the same period were tested using Student t test for continuously distributed variables and Pearson χ² test for dichotomous variables; differences of incidence and mortality between 3 periods in men and women were estimated using linear trend test. Trends in age-standardized incidence of stroke were calculated from annual percentage of change by the regression model log(r)=a+b·t, where log denotes the natural logarithm and t is the year. The trend b was estimated from the ordinary regression, and 100b represents the estimated annual percentage of change of incidence. In addition, we analyzed the changes in levels of cardiovascular disease risk factors between 1991 and 2011. Statistical significance was inferred by P<0.05. SPSS for Windows (version 15.0; SPSS Inc, Chicago, IL) was used for the analyses.

Results
Descriptive Characteristics of Patients With Stroke
We followed 304,260 person-years in total, and the proportion of migration in this study population was 0.23% annually during 1992 to 2012. Overall, 908 patients experienced stroke, 542 men (60%) and 366 women (40%). The proportion of strokes that occurred by age group was significantly different in men compared with women during 1992 to 1998; there were more women (30; 46%) than men (33; 29%) in 45- to 64-year age group; more men (76; 67%) than women (31; 48%) were in ≥65-year age group (P<0.001). The mean age at first-ever stroke in women (64±12 years) was 4 years younger than in men (68±11 years) in 1992 to 1998 (P=0.024), but not in 1999 to 2005 and 2006 to 2012. The proportion of diagnosis by imaging (computed tomography/MRI) improved during the 3 study periods, with no difference between men and women observed (Table 1).

Sex Differences in Secular Trend of Age-Standardized Incidence of Stroke and Male/Female Rate Ratio by Age and Period
The age-standardized incidence of first-ever stroke increased steadily in both men (166 in 1992–1998, 227 in 1999–2005, and 376 in 2006–2012 per 100,000 person-years) and women (86 in 1992–1998, 148 in 1999–2005, and 264 in 2006–2012 per 100,000 person-years) during the past 21 years (P<0.001) and were higher in men than in women overall (P<0.001) and age ≥65 years (P<0.001, 0.004, 0.046, respectively). The male/female rate ratio (95% confidence interval) revealed a significant trend of decline over time.
Annual Proportion of Change in Incidence in First-Ever Stroke by Age
Between 1992 and 2012, the incidence of first-ever stroke increased by 5.8% in men and 8.0% in women annually and by 6.4% in women and 2.7% in men aged ≥65 years.

Secular Trend in Mortality <30 Days of First-Ever Stroke by Age and Period
There were no significant sex differences in trends of stroke mortality by age throughout the entire study period (Table 3).

Trends in Cardiovascular Risk Factors in the Study Population From 1991 to 2011
The prevalence of hypertension, diabetes mellitus, obesity, and alcohol consumption was significantly higher in 2011 than in 1991, both in men and in women; the prevalence of smoking, in contrast, decreased in men. The prevalence of obesity appeared significantly higher in women than in men in 2011.
Sex Differences in Stroke Incidence Trends, China

1991 (8.2% versus 2.5%; P<0.001) as well as in 2011 (21.4% versus 17.7%; P=0.004). There was a higher prevalence of diabetes mellitus in women than in men for overall (P=0.002) and those aged 45 to 64 years (P<0.001) in 1991. The prevalence of diabetes mellitus in women aged ≥65 years in 2011 increased by 12.8× compared with 1991 (8.3% versus 0.6%; P<0.001). The prevalence of smoking obviously decreased in men (37% versus 46%; P<0.001) from 1991 to 2011, but the prevalence of alcohol consumption increased in both sexes (P<0.001). The level of fasting glucose was lower in women than in men in 1991, and total cholesterol was higher in women than in men in 2011 (P=0.002). Illiteracy rate also was higher in women than in men both in 1991 (P=0.029) and in 2011 (P<0.001), but increased significantly from 1991 to 2011 in both sexes (P<0.001). The age of menopause and reproductive years in women increased significantly during the past 2 decades (P<0.001 and 0.006; Table 4).

Discussion

We observed a greater annual increasing proportion in women than in men (8.0% versus 5.8%) and a trend of declined male/female rate ratio in the incidence of first-ever stroke among those aged ≥65 years in our large population-based longitudinal study although the incidence of first-ever stroke was higher in men than in women.

Sex differences in stroke incidence and mortality have been reported.4,5,15,16 There was a lower incidence of stroke in women than in men17–19; however, the incidence and mortality of stroke were found to be higher in older women than in older men.20–22 Consistent with the findings in Western populations, in this study the incidence of stroke was lower in women than in men for all age groups, and the male/female incidence ratios declined over time, especially in those aged ≥65 years (from 2.6 to 1.6 to 1.3). Moreover, some studies found declines in stroke incidence to be greater in men.16,23–25 We observed, nevertheless, that the incidence of stroke, annually, was greater in women than in men (8.0% versus 5.8%) from 1992 to 2012; although we did not observe significant sex differences in 30-day mortality, it is reverse to previous research.9 This is the first report to find a greater increase in stroke incidence among women over men in China.

In women, the higher annual percentage of change may, in part, be responsible for the obvious increased prevalence of hypertension, obesity, diabetes mellitus, and the levels of total cholesterol and triglycerides during 1991 to 2011. A 12.8× increased prevalence of diabetes mellitus in women aged ≥65 years may partly explain the significant declined in male/female incidence ratio in those aged ≥65 years.

In addition, we observed that women developed a first-ever stroke on average 4 years earlier than in men in 1992 to 1998, but no difference was observed in 1999 to 2005 and 2006 to 2012.

Table 3. Sex Differences in Age-Standardized Mortality <30 Days by Age in the Tianjin Brain Study (%)

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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>&lt;45 y</td>
<td>25</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>45–64 y</td>
<td>6.1</td>
<td>16.7</td>
<td>0.3 (0.1,1.8)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>31.6</td>
<td>25.8</td>
<td>1.3 (0.6,2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>23.9</td>
<td>20.0</td>
<td>1.3 (0.6,2.6)</td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>8.1</td>
<td>14.7</td>
<td>0.5 (0.1,2.3)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>31.6</td>
<td>25.8</td>
<td>1.3 (0.6,2.6)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and RR, relative risk.
This is not in accordance with the findings of most previous studies that women tend to develop first-ever stroke at an older age compared with men.\(^\text{15,22,26–28}\) The younger age of stroke among women in the early period of this study could not be explained with the present population-based studies or associated with protective sex hormones.\(^\text{29–31}\) Previous research has found that women were protected from stroke relative to men up until menopause.\(^\text{31}\) Unsurprisingly, we observed a younger age of menopause and short reproductive years in 1991 compared with 2011, which resulted in the earlier disappearance of protective sex hormones. In our study, we observed a higher prevalence of obesity and diabetes mellitus in women than in men among those aged 45 to 64 years in 1992 to 1998. Lower education level is also associated with increased stroke risk in middle-aged women; it is partially mediated by known risk factors, particularly lifestyle and biological factors.\(^\text{32}\) Diabetes mellitus and obesity are clearly important risk factors for stroke.\(^\text{33–35}\) A higher proportion of illiteracy and a higher prevalence of diabetes mellitus and obesity in women than in men may partially explain the sex differences in stroke incidence during the early period. The link between education and stroke is a novel finding in this population, because no previous studies have reported it in China.

Our study was restricted to a county sample in northern China, which limits the generalization of our results. Cardiovascular risk factors were only monitored twice during the study. The low percentage of imaging by brain computed tomographic scan during the early period of 1992 to 1998 may lead to over- or underestimation of the incidence of stroke and limits further analysis for stroke subtypes. However, the present study also has numerous strengths: first is the availability of >21 years of prospective follow-up data from the large population-based longitudinal study design; second is the high efficiency of follow-up by village doctors, and the restricted living area of every participant provided thorough follow-up registration of stroke events and mortality during the past 21 years; third is ≥100,000 person-years of observations were recorded in all 3 study periods, fulfilling the criteria for population studies of stroke incidence.\(^\text{36}\)

Our study provides the first longitudinal data on sex differences in stroke incidence during a 21-year period in a low-income rural area in China. There has recently been a remarkable increase in the incidence of stroke in women compared with men. Sex disparities in stroke incidence indicate that more attention should be given to cardiovascular health prevention in women in China, such as the Go for Red campaign initiated by the American Heart Association. We also found a concurrent increase in the levels of stroke-related risk factors. Our data suggest that stroke will eventually become the major disease with the highest impact on women; the incidence of stroke in China may continue to increase.

### Table 4. Sex Differences in Prevalence of Related Risk Factors Among Study Population in the 1991 and 2011 Surveys

<table>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n (%)</td>
<td>1032 (47)</td>
<td>1164 (53)</td>
<td>865 (45)</td>
<td>1074 (55)</td>
</tr>
<tr>
<td>Illiterate, n (%)</td>
<td>312 (30)</td>
<td>470 (40)</td>
<td>56 (6)</td>
<td>217 (20)</td>
</tr>
<tr>
<td>Hypertension*, %</td>
<td>39 (37, 41)</td>
<td>41 (38, 44)</td>
<td>50 (47, 54)</td>
<td>54 (51, 57)</td>
</tr>
<tr>
<td>&lt;45 y</td>
<td>24 (19,28)</td>
<td>24 (20,27)</td>
<td>31 (25,37)</td>
<td>40 (32,48)</td>
</tr>
<tr>
<td>45–64 y</td>
<td>42 (38,47)</td>
<td>45 (41,50)</td>
<td>59 (54,63)</td>
<td>58 (54,61)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>66 (58,74)</td>
<td>71 (64,79)</td>
<td>68 (62,75)</td>
<td>74 (68,80)</td>
</tr>
<tr>
<td>Obesity*, %</td>
<td>3 (0, 9)</td>
<td>8 (3, 14)</td>
<td>18 (15, 20)</td>
<td>21 (16, 26)</td>
</tr>
<tr>
<td>&lt;45 y</td>
<td>2 (1, 3)</td>
<td>7 (5, 9)</td>
<td>17 (12, 22)</td>
<td>19 (12, 24)</td>
</tr>
<tr>
<td>45–64 y</td>
<td>3 (2, 9)</td>
<td>10 (7,12)</td>
<td>18 (15,22)</td>
<td>22 (19,25)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>4 (1, 6)</td>
<td>7 (3, 11)</td>
<td>18 (13, 24)</td>
<td>21 (16, 27)</td>
</tr>
<tr>
<td>Diabetes mellitus*, %</td>
<td>1 (0, 8)</td>
<td>3 (0, 9)†</td>
<td>4 (0,10)</td>
<td>6 (0, 9)</td>
</tr>
<tr>
<td>&lt;45 y</td>
<td>1 (0, 2)</td>
<td>3 (1, 4)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>45–64 y</td>
<td>2 (1, 3)</td>
<td>5 (3,7§§)</td>
<td>5 (3, 7)</td>
<td>6 (4, 8)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
<td>4 (2, 7)</td>
<td>8 (4,12)</td>
</tr>
<tr>
<td>Smoking*, %</td>
<td>46.0 (41,6, 50.5)</td>
<td>3.7 (0, 9.3)†</td>
<td>36.8 (31,5, 42.2)</td>
<td>4.8 (0, 10.6)†</td>
</tr>
<tr>
<td>Alcohol consumption*, %</td>
<td>18.9 (13.4, 24.4)</td>
<td>0.3 (0, 6.0)†</td>
<td>31.6 (26.1, 31.6)</td>
<td>4.5 (0, 10.3)†</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.8 (1.5)</td>
<td>4.6 (0.9)†</td>
<td>5.2 (1.7)</td>
<td>5.3 (1.8)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.3 (0.9)</td>
<td>4.3 (1.0)</td>
<td>4.6 (1.1)</td>
<td>4.8 (1.2)†</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
<td>1.5 (1.1)</td>
<td>1.6 (1.0)</td>
</tr>
<tr>
<td>Age of menarche, y</td>
<td>…</td>
<td>16.3 (1.8)</td>
<td>…</td>
<td>16.3 (2.0)</td>
</tr>
<tr>
<td>Age of menopause, y</td>
<td>…</td>
<td>48.6 (3.6)</td>
<td>…</td>
<td>49.8 (3.0)</td>
</tr>
<tr>
<td>Reproductive years, y</td>
<td>…</td>
<td>32.3 (4.2)</td>
<td>…</td>
<td>33.2 (3.4)</td>
</tr>
</tbody>
</table>

*Prevalence of hypertension, diabetes mellitus, obesity, smoking, drinking are expressed as rate (95% confidence interval), and age of menarche, age of menopause, and reproductive years are expressed as mean (SD).

†P<0.001; ‡P<0.01; §P<0.05 on a χ² test/t test between men and women during the study periods.
in future decades, without immediate implementation of an efficient policy controlling the relevant cardiovascular risk factors.

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