Higher Stroke Incidence in the Spring Season Regardless of Conventional Risk Factors
Takashima Stroke Registry, Japan, 1988–2001
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Background and Purpose—Seasonal variation in stroke incidence was examined using 14-year stroke registration data in a Japanese population. We also examined if this variation was modified by conventional stroke risk factors hypertension, diabetes mellitus, drinking, and smoking.

Methods—Data were obtained from the Takashima Stroke Registry, which covers a stable population of ≈55,000 in Takashima County in central Japan. There were 1665 (men, 893; women, 772) registered first-ever stroke cases during 1988 to 2001. The average age of stroke onset for men and women patients was 69.4 and 74.2 years, respectively. Incidence rates (per 100,000 person-years) and 95% CI were calculated by gender, age, and stroke subtype for winter, spring, summer, and autumn. After stratifying patients by their risk factor history, the OR (with 95% CI) of having a stroke in autumn, winter, and spring were calculated, with summer serving as a reference.

Results—Among the seasons, stroke incidence per 100,000 person-years was highest in the spring (231.3; 95% CI, 211.1 to 251.5). Spring incidence was highest in both men (240.8; 95% CI, 211.5 to 270.2) and women (222.1; 95% CI, 194.4 to 249.9), and in subjects younger than 65 years (72.6; 95% CI, 60.0 to 85.3) and 65 years or older (875.9; 95% CI, 787.5 to 964.3). Among stroke subtypes, spring incidence was highest for cerebral infarction (154.7; 95% CI, 138.2 to 171.2) and cerebral hemorrhage (53.7; 95% CI, 44.0 to 63.4). The spring excess in stroke incidence was observed regardless of the presence or absence of the risk factor histories.

Conclusions—Stroke incidence appears to be highest in the spring among a Japanese population regardless of conventional risk factor history. Factors that explain this excess need further investigation. (Stroke. 2008;39:745-752.)

Key Words: epidemiology ■ incidence ■ risk factor ■ season ■ stroke

A seasonality of stroke incidence has been reported in various parts of the world.1–13 Studies have reported an increase in stroke incidence, mortality, and stroke hospitalization during the colder months of winter and spring and a decrease during the warmer summer and autumn.1–11 However, other studies have found no apparent seasonal trend in stroke incidence.12,13 Although a few studies in Japan have reported a seasonal variation in stroke incidence,8–10 these studies were primarily hospital-based,9 of shorter duration,8,9 or included a small numbers of stroke events.10 In contrast, a stroke registry of long duration covering an entire population would be most suitable for addressing issues such as a seasonal variation in stroke incidence. A population-based stroke registry also has the potential for generating information on the diverse characteristics of strokes related to geographical, demographical, and environmental influences. Although it is well-established that stroke incidence is affected by risk factors such as hypertension, diabetes mellitus, cigarette smoking, and alcohol intake,14 the effects of these risk factors on a seasonal variation in stroke incidence have not been clearly addressed. Information about seasonal trends regarding episodes of increased stroke incidence and how these trends are influenced by conventional stroke risk factors might be used as a surrogate to predict stroke onset and might be helpful in preparing awareness messages during periods of increased stroke risk.

In the present study we examined the seasonal variation in stroke incidence using data from the Takashima Stroke Registry that covers a stable population of ≈55,000 individuals in central Japan. We also examined the modification of...
these seasonal variations by history of traditional risk factors. We considered the role of hypertension, diabetes mellitus, cigarette smoking, and alcohol intake in contributing to any excesses in stroke incidence during seasons when stroke risk might be highest.

**Methods**

**Takashima Stroke Registry**

Takashima Stroke Registry is the integrated part of the Takashima Cardiocerebrovascular Disease Registration System established in 1988 in Takashima County, Shiga, Japan. The objective of this disease registration system for stroke is to measure trends in the incidence and case fatality of stroke and to compare these to sources inside and outside of Japan. 

**Topography and Climate of the Registration Area**

Takashima County is located in the rural part of Shiga prefecture in the central part of Japan. The largest freshwater lake in Japan, Biwako Lake, popularly known as Lake Biwa, is located to the east of Takashima County stretching from north to south. In addition, the Mount Hira mountainous belt, locally called Hira-san, runs north and south to the west. The weather in Shiga, as with central Japanese weather, follows 4 very distinct seasons: winter, spring, summer, and autumn. There are early spring rains in April, a rainy period between mid June to mid July, autumn rains in September, and typhoons before and after September. There are also snowfalls between December and February. Takashima County is located at ~35° north and 136° east. The average annual temperature is ~13.5°C, ranging from 2.5°C in February to 29.5°C in August. The annual precipitation is ~175 cm, with the highest monthly averages in June (22 cm).

**Population Characteristics of the Registration Area**

The population of Takashima County remained stable during the 14-year study period. It is a community with inhabitants mainly classified culturally into a single subgroup and with similar standards of living. With an aging populace, the population included 55 451 inhabitants (men, 49.2%; women, 50.7%) in the year 2000. Among the population, 22.3% were aged 65 or older, which is higher than the all Japan proportion of 17.4%.

**Case Finding and Registration Process**

The registered patients included all residents of the Takashima County who were hospitalized with stroke in the county hospitals. Stroke patients who were residents of Takashima County but visited or were referred to 1 of the 3 tertiary hospitals outside the county were also included in the registry. Registered stroke patients were monitored annually by death certification. Original death certificates were seen at the county health center with the permission of the Ministry of Public Management, Home Affaires, Post and Telecommunications, Japan, to establish the cause of death. Patient privacy was protected. Approvals for this study regarding ethical issues were obtained from the Institutional Review Boards of the Shiga University of Medical Science, the participating hospitals, as well as from the administration of Takashima County. Stroke was defined as sudden onset of neurological symptoms, which continued for a minimum of 24 hours or resulted in death. Diagnosis of stroke type was based on clinical symptoms as well as neurological imaging by CT or MRI. Stroke was categorized into cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, and unclassified stroke. Items recorded at registration of a stroke were the date and time of stroke onset, the situation and symptoms at the event, the extent of neurological symptoms and clinical observations at the event, history, family history, treatment given, rehabilitation, fatality, cause of death, recurrence in acute stage, neurological imaging observations, and so forth. Details of the case finding, registration process, diagnostic criteria, and items registered have been described elsewhere.

**Statistical Methods**

Our analysis included all patients from the Takashima Stroke Registry who experienced their first ever stroke irrespective of outcome. The period of the present study covered the time period from January 1, 1988 to December 31, 2001. During this 14-year period (5114 days, leap years also taken into account), the seasonal variation of stroke incidence was examined by comparing incidence rates within several groups. The year was divided into 4 seasons: winter, included December, January, and February; spring included March, April, and May; summer included June, July, and August; and autumn included September, October, and November. To examine the effect of age on the patterns of stroke incidence, patients were stratified into groups younger than 65 and those 65 years or older at the time of stroke onset.

Incidence rates of stroke per 100 000 person-years, including 95% CI, were measured among the 4 seasons by gender, age group and stroke subtype. To calculate the incidence, the total number of stroke events was divided by the person-years of subjects at risk within Takashima County across the 14 years of available data within a season. For example, the person-years for spring was calculated by multiplying the population average in Takashima County by 14 years after weighting by the number of days in the spring season (1288 days). We calculated the population average by averaging the population census for each year for the years 1988 to 2001 for the relevant group. The population demographic data derived from the routine census and vital statistics system are collected annually for the Takashima County for each of the years of the study period. These provide the precise denominator for the calculations of rates.

Stroke incidence was categorized as having occurred in winter, spring, summer, or autumn, based on its day of onset. Using multinomial logistic regression, stroke case across season was modeled as a dependent variable. From such models, 3 regression coefficients were estimated, which provide estimates of the OR of stroke occurring in the winter, spring, and autumn versus the summer as a reference. The OR was calculated as $e^{\beta}$ with 95% CI = $e^{\beta \pm 1.96\text{SE}}$. Here, $\beta$ is the regression coefficient corresponding to winter, spring, or autumn (with summer as a reference), and “SE” is the standard error of $\beta$. The ORs were calculated separately within gender, age group, risk factor strata (presence or absence of a history of hypertension, diabetes mellitus, and drinking and smoking status), and by stroke subtype. In other analyses, risk factors were modeled as independent variables to further examine the possible effect of interactions between risk factors on the seasonal occurrence of stroke.

Among the risk factors, information on hypertension, diabetes mellitus, cigarette smoking, and alcohol drinking were missing in 13.0%, 14.8%, 25.5%, and 29.8% of the stroke cases, respectively. To determine whether seasonal stroke patterns were different in individuals without information on risk factor histories, ORs (and 95% CIs) were also calculated for those whose risk factor data were missing.

All statistical analyses were performed using SPSS for windows, version 13.0 (SPSS Inc) and SAS version 9.1 (SAS Institute).

**Results**

Table 1 shows the characteristics of the registered stroke cases from 1988 to 2001. A total of 1665 stroke cases (men, 893; women, 772) were registered during the study period of 1988 to 2001. The average age of the registered patients at stroke onset was 69.4 years in men and 74.2 years in women. Most of the cases were classified as cerebral infarction (1131; men, 654; women, 486) and cerebral hemorrhage (352; men, 171; women, 181). There were 30 stroke cases (1.8%) with a history of myocardial infarction. The average age at stroke onset did not vary significantly across the seasons.

Table 2 shows the incidence rates of stroke and its subtypes across the seasons. The incidence rate of stroke was highest in the spring (231.3 per 100 000 person-years; 95% CI, 211.1 to
251.5) and lowest in the summer (183.1; 95% CI, 165.2 to 201.1). An excess stroke incidence in the spring was observed in both men (240.8; 95% CI, 211.5 to 270.2) and women (222.1; 95% CI, 194.4 to 249.9), and in subjects younger than 65 years (72.6; 95% CI, 60.0 to 85.3) as well as subjects 65 years or older (875.9; 95% CI, 787.5 to 964.3). A spring excess of stroke incidence was observed for both cerebral infarction (154.7; 95% CI, 138.2 to 171.2) and cerebral hemorrhage (53.7; 95% CI, 44.0 to 63.4).

Figure 1 presents the OR of a stroke stratified by stroke subtype, gender, and age for autumn, winter, and spring, with summer as a reference. Among all strokes, the spring excess was significantly higher compared with the summer. In addition, the ratio of stroke risk in the spring compared with the summer for cerebral infarction and cerebral hemorrhage was 1.21 (95% CI, 1.03 to 1.43) and 1.47 (95% CI, 1.09 to 1.97), respectively. For women, the stroke risk was 1.50 (95% CI, 1.22 to 1.84) times higher in spring than the summer. Among older stroke victims (65 years or older), stroke risk was 1.27 (95% CI, 1.09 to 1.48) times higher in spring than the summer.

Figure 2 presents the OR of a stroke stratified by the presence or absence of a history of risk factors (hypertension, diabetes mellitus, smoking, and drinking) for autumn, winter, and spring, with summer as a reference. Regardless of the presence or absence of a history of these risk factors, there was an elevated stroke risk in the spring. Although the sample size and statistical power were reduced within each of the risk-factor strata, a significantly elevated stroke risk continued to be observed in the absence of diabetes mellitus and in nondrinkers and nonsmokers. Although among the risk factors the seasonal distributions were not exactly similar, in all instances, the highest risk of stroke still occurred in the spring relative to the other seasons. Whereas sample size and statistical power are limited, we found a similar pattern of seasonal stroke incidence that appeared in those with and without missing data.

Figure 3 presents the OR of a stroke for the seasonal comparisons after adjustment for a history of hypertension, diabetes mellitus, smoking, and drinking status. Differences from Figure 2 are modest. Whereas risk factor interactions were also assessed, none was statistically significant. This latter finding, however, could be a consequence of limited statistical power.

**Discussion**

The present study shows a seasonal variation in the incidences of stroke events in both men and women and in younger and older age groups. Stroke incidence was highest in the spring (183.1; 95% CI, 165.2 to 201.1). An excess stroke incidence in the spring was observed in both men (240.8; 95% CI, 211.5 to 270.2) and women (222.1; 95% CI, 194.4 to 249.9), and in subjects younger than 65 years (72.6; 95% CI, 60.0 to 85.3) as well as subjects 65 years or older (875.9; 95% CI, 787.5 to 964.3). A spring excess of stroke incidence was observed for both cerebral infarction (154.7; 95% CI, 138.2 to 171.2) and cerebral hemorrhage (53.7; 95% CI, 44.0 to 63.4).

**Table 1. Population and Registered Stroke Patients of Takashima Stroke Registry, Shiga, Japan, 1988–2001**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Takashima County Population* N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>55 451</td>
</tr>
<tr>
<td>Men</td>
<td>27 323 (49.2)</td>
</tr>
<tr>
<td>Women</td>
<td>28 128 (50.7)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>43 081 (77.7)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>12 354 (22.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Registered Stroke Cases</th>
<th>Men</th>
<th>Women</th>
<th>All Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total incidence</td>
<td>893</td>
<td>772</td>
<td>1665</td>
</tr>
<tr>
<td>Average year at onset (yr)</td>
<td>69.4</td>
<td>74.2</td>
<td>71.6</td>
</tr>
<tr>
<td>SD</td>
<td>11.9</td>
<td>12.0</td>
<td>12.2</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>280</td>
<td>139</td>
<td>419</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>613</td>
<td>633</td>
<td>1246</td>
</tr>
</tbody>
</table>

**Table 2. Incidence Rate (per 100 000 person-yr) for Stroke for Seasons by Gender, Age Group, and Subtype in the Takashima Stroke Registry, Shiga, Japan, 1988–2001**

<table>
<thead>
<tr>
<th></th>
<th>Winter (95% CI)</th>
<th>Spring (95% CI)</th>
<th>Summer (95% CI)</th>
<th>Autumn (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>214.8 (195.1–234.4)</td>
<td>231.3 (211.1–251.5)</td>
<td>183.1 (165.2–201.1)</td>
<td>190.7 (172.3–209.2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>224.6 (195.9–253.2)</td>
<td>240.8 (211.5–270.2)</td>
<td>217.5 (189.6–245.4)</td>
<td>203.9 (176.7–231.0)</td>
</tr>
<tr>
<td>Women</td>
<td>205.3 (178.3–232.2)</td>
<td>221.2 (194.4–249.9)</td>
<td>149.9 (127.1–172.7)</td>
<td>178.0 (153.0–203.0)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;64 years</td>
<td>61.8 (50.0–73.6)</td>
<td>72.6 (60.0–85.3)</td>
<td>57.2 (45.9–68.4)</td>
<td>61.3 (49.6–72.9)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>836.0 (748.8–923.2)</td>
<td>875.9 (787.5–964.3)</td>
<td>694.7 (615.9–773.4)</td>
<td>716.4 (635.9–796.8)</td>
</tr>
<tr>
<td><strong>Stroke subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>149.3 (132.9–165.6)</td>
<td>154.7 (138.2–171.2)</td>
<td>127.6 (112.6–142.6)</td>
<td>120.7 (106.0–135.3)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>42.1 (33.4–50.8)</td>
<td>53.7 (44.0–63.4)</td>
<td>37.2 (29.1–45.3)</td>
<td>44.5 (35.6–53.5)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>21.5 (15.3–27.7)</td>
<td>18.8 (13.4–24.6)</td>
<td>16.5 (11.1–21.9)</td>
<td>21.3 (15.2–27.5)</td>
</tr>
</tbody>
</table>

*Data are based on the population census of Japan for the year 2000 (age reported unknown for 16 persons).
Figure 1. The ORs and 95% CIs are shown for the occurrence of stroke stratified by stroke subtype, gender, and age in autumn (September, October, and November), winter (December, January, and February), and spring (March, April, and May) compared with summer (June, July, and August). Takashima Stroke Registry, Shiga, Japan (1988–2001).
in the spring, followed closely by the winter. A similar seasonal pattern was observed for both cerebral infarction and cerebral hemorrhage. This pattern seems to hold regardless of the presence and absence of a history of risk factor histories, including hypertension, diabetes mellitus, smoking, and drinking.

Our findings are similar to other studies in Japan, where stroke incidence was found to be higher during the winter and spring. Among reports from studies outside of Japan, there also is evidence that the incidence of stroke peaks in the winter and spring, with a trough in the summer and autumn seasons. Similar to the findings of others, we did not observe any seasonal pattern for subarachnoid hemorrhage, although this in part could have been attributable to the small numbers of these events. Although Shinkawa et al describe seasonality according to months within a year, their findings

Figure 2. The ORs and 95% CIs are shown for the occurrence of stroke stratified by the presence and absence of a history of hypertension, diabetes mellitus, drinking, and smoking status in autumn (September, October, and November), winter (December, January, and February), and spring (March, April, and May) compared with summer (June, July, and August). Takashima Stroke Registry, Shiga, Japan (1988–2001). ORs are also given for those with missing data.
are comparable and in agreement with the current report. In our study, however, the spring excess in stroke incidence appeared to be present regardless of the presence or absence of history of hypertension, diabetes mellitus, drinking, and smoking. This pattern seems to hold after adjusting for risk factor histories as independent variables. All stroke seasonal distribution showed significant distribution across seasons, but after stratifying for risk factor status significant excess continued to be observed in the absence of diabetes mellitus and in nondrinkers and nonsmokers. In instances of the other risk factor status significance was no longer present; however, findings could in part be attributed to a large reduction in sample size because of missing data and a loss of statistical power. It was also observed that the proportion of the presence or absence within the risk factors did not vary across the seasons. Hence the prevalence of risk factors for stroke was quite similar among the 4 seasons, indicating that the spring peak pattern of the stroke incidence holds irrespective of the risk factor histories.

This present study is based on a registry data, thus a community-based surveillance system data, which do not assist in exploring the mechanisms or causes related to the seasonal variation of stroke. Now identifying the seasonal trend, an interesting area for investigation will be the relationship of variations in physical activity and environmental factors and stroke occurrence among seasons using longitudinal data.

The mechanisms underlying seasonal variation of strokes are not fully understood. The weather component factors could serve as a set-off factor for stroke. The physiological processes related to these weather components may trigger the acute stroke event. Among seasons, variation in temperature has been considered to be the most likely reason to influence the stroke incidence. Probable explanations for seasonal variation in stroke incidence include seasonal variation of biological factors such as blood pressure, serum lipids, some blood components, and hypercoagulable state (plasma fibrinogen concentration and viscosity). Seasonal pattern of influenza epidemic, air pollution, and other respiratory tract infections also are presumed to influence the seasonality of the stroke and cardiovascular incidence.

The seasonal fluctuation in blood pressure is very similar to that for stroke with blood pressure having an elevation in colder weather and a trough in warmer conditions. Sustained higher level of blood pressure during the colder weather might be associated with increased risk of stroke occurrence. Furthermore, serum cholesterol, C-reactive protein, factor VII activity, red blood cells, and platelet

![Graphs showing odds ratios for adjusted conditions](Figure 3. The ORs and 95% CIs are shown for the occurrence of stroke adjusted for a history of hypertension, diabetes mellitus, drinking, and smoking in autumn (September, October, and November), winter (December, January, and February), and spring (March, April, and May) compared with summer (June, July, and August). Takashima Stroke Registry, Shiga, Japan (1988–2001).)
count\textsuperscript{29} are all higher in colder weather. Elevation of these parameters may contribute to an increased tendency toward arterial thrombosis and a higher incidence of cardio-cerebrovascular disease.\textsuperscript{22,30} Plasma fibrinogen concentration and viscosity show considerable seasonal variations, at least in elderly individuals,\textsuperscript{28} and it has been reported that fibrinogen is a significant stroke predictor.\textsuperscript{31} Infection, particularly influenza epidemics and other respiratory tract infections,\textsuperscript{22,32} may also play a role. Influenza may cause some complications in atherosclerotic disease and induce hypercoagulation.\textsuperscript{34} In Japan, peak influenza activity in the winter and early spring coincides with peak stroke incidence.

Psychological stress is reported to be a significant risk for stroke and coronary artery disease, even after adjustment for other established risk factors in middle-aged men.\textsuperscript{35,36} Regarding cardiovascular and cerebrovascular sudden death, it has been reported that in Japanese working population it occurred more frequently in April, when the new business year starts, compared to other months.\textsuperscript{37} It was hypothesized that younger people in Japan might have to face greater occupational stress at the end of the old financial year and the beginning of the new year coinciding with winter and spring.\textsuperscript{10,37}

The quality of our registration system was assured by its completeness. Our registry system was planned to capture all the cases in the study area by covering all the hospitals of the county. It has been estimated that >98\% of all hospital admissions of Takashima County are seen in these institutions.\textsuperscript{15} To ensure that eligible patients hospitalized outside the county were not left out, registration procedures were also conducted at 3 high-level medical facilities outside the county.

In Japan almost 100\% of the residents are covered by health insurance under the control of Ministry of Health and Welfare.\textsuperscript{15,38} People with mild stroke who visited general physicians in the community are almost always referred to secondary or tertiary level hospitals for extensive investigations. In addition to that, 24-hour emergency ambulance service is available for residents without any charge. The usual practice in Japan is to take patients with any acute disease conditions to the emergency facilities. Thus, we believe that extremely few patients would be left out of our registration system.

Japan has the most MRI units (35 units per million population) and CT scanners (93 units per million population) per capita among the developed countries.\textsuperscript{39} In our registered stroke cases, the diagnoses were verified by neurological imaging in 93.3\% cases. Of these cases, 58.8\% had CT alone, 37.2\% had both CT and MRI, and 4.2\% had MRI alone. Therefore, in our registration system, identification of stroke cases among the study area was almost complete and stroke categorization was highly accurate.

It has been suggested that the increase in stroke events during the colder weather might be an artifact of the registration process attributable to referral bias.\textsuperscript{12} However, the health care system in Japan covers and ensures treatment availability for all the residents and the round-the-clock free of charge emergency ambulance service ensures all hospital transfers. Also, the standard practice in Japan is to take patients with any acute disease conditions to the emergency facilities. Thus, these unique characteristics of the Japanese health care system minimized the influence of referral bias in our registry.

The main limitation of our study is the missing information for a number of registered patients regarding their history of risk factors such as hypertension, diabetes mellitus, smoking, and drinking. Even after examining individuals with missing risk factor information, there was a similar pattern of seasonal stroke incidence that appeared in those without missing data. We also could not determine the disease duration for hypertension and diabetes mellitus or quantify the amount of alcohol or cigarette smoking, both in cases of habitual quantity or just before the stroke onset. Rather, we used information reported about presence or absence of the risk factor history. An additional limitation is that the Takashima Stroke Registry covers a rural and semi-urban population in Japan that may be different from the metropolitan population.

In conclusion, we found that there was increased stroke incidence during the spring, followed by winter. This was observed in both young and old subjects and in both men and women. This spring excess of stroke incidence was observed for both in the presence and absence of conventional risk factors. Thus, our analysis points toward an influence of internal or external stroke-triggering factors in the time preceding acute onset of stroke. The identity of these triggering factors, which may be of significant use in stroke prevention strategies, requires further investigation.

Acknowledgments

The authors thank Tomomori Okamura, MD, and Atsushi Hozawa, MD, of Department of Health Science, Shiga University of Medical Science, for statistical advice and critical review of the manuscript.

Sources of Funding

This study was supported in part by grants from The Research on Cardiovascular Disease (3A-1, 6A-5, and 7A-2) and The Comprehensive Research on Cardiovascular and Life Style Related Diseases (H18-CVD-Ippan-029) of Ministry of Health and Welfare, and from the grants-in-aid Scientific Research (C-213670361 and B-17390186) of Ministry of Education, Culture, Sports, Science, and Technology and Japan Society for the Promotion of Science.

Disclosures

None.

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Tanvir Chowdhury Turin, Yoshikuni Kita, Yoshitaka Murakami, Nahid Rumana, Hideki Sugihara, Yutaka Morita, Nobuyoshi Tomioka, Akira Okayama, Yasuyuki Nakamura, Robert D. Abbott and Hirotsugu Ueshima

Stroke. 2008;39:745-752; originally published online February 7, 2008; doi: 10.1161/STROKEAHA.107.495929
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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