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Background—The study of long-term trends in the incidence of and risk factors for ischemic stroke subtypes could offer insights into primary and secondary prevention.

Methods and Results—We established 3 cohorts of residents ≥40 years of age in 1961, 1974, and 1988 in the Japanese community of Hisayama. Morphological examinations by autopsy or brain imaging were performed on most of the ischemic stroke cases developed in these cohorts. When 13-year follow-up data were compared, the age-adjusted incidence of ischemic stroke and lacunar infarction declined significantly from the first to the third cohort for both sexes, whereas the incidences of atherothrombotic and cardioembolic infarction did not change during this period. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. A rapid increase in the prevalence of metabolic disorders may have offset the impact of improvements in hypertension control and resulted in a slowdown of the decline in the incidence of ischemic stroke in the cohorts in the present study; however, hypertension still makes a large contribution to the development of ischemic stroke.

Conclusions—These findings suggest that in the Japanese population, the incidence of ischemic stroke has declined significantly over the past 40 years, probably owing to better management of hypertension. There is a need for greater primary prevention efforts in the treatment of hypertension and metabolic disorders. (Circulation. 2008;118:2672-2678.)

Key Words: cerebral infarction • morbidity • risk factors • hypertension • trend

Stroke continues to be a major public health concern worldwide. In Japan, it is the third leading cause of death and a major neurological cause of long-term disability.¹ The increase in the elderly population that accompanies the improvement in life expectancy is expected to further increase stroke prevalence. On the other hand, there have been major advances in the identification and management of stroke risk factors and the treatment of acute stroke. The study of temporal trends in stroke incidence provides insights into the effect of these factors. Several epidemiological studies have reported that the declining or stable incidence of stroke is likely attributable to better treatment of risk factors over time.²⁻⁸ On the basis of their 50 years of follow-up data, the authors of the Framingham Study recently showed that the age-adjusted incidence of stroke decreased significantly in men and women owing to the improved control of hypertension and smoking.⁵ In Japan, the incidence of stroke declined by 60% from 1964 to 1983 in a rural population.⁷ We also found in a Japanese urban area that the incidence of ischemic stroke declined markedly between the 1960s and 1970s as a result of hypertension control, but this declining trend was slowed in the late 1980s and 1990s, probably because of an increase in metabolic disorders.⁸

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Because the pathogenesis, prognosis, and treatment differ among ischemic stroke subtypes,⁹,¹⁰ the evaluation of temporal trends in the incidence of and risk factors for ischemic stroke subtypes may contribute to more effective primary and secondary prevention of ischemic stroke. However, morphological features of the brain were not readily available before the widespread use of computed tomography and magnetic resonance imaging, and the definition of ischemic stroke subtypes was not determined until the early 1990s.¹¹⁻¹³ Therefore, there is little information on the effect of the changes in cardiovascular risk factors on secular trends in the incidence of ischemic stroke and its subtypes.

The Hisayama Study is a population-based study that has established several cohorts at times that correspond to periods of remarkable lifestyle changes in Japan.⁸,¹⁴⁻¹⁶ One of the

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.107.743211

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characteristics of this study is that most of the deceased study subjects underwent autopsy examination from the beginning of the study, and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort. Furthermore, study-team physicians performed physical and neurological examinations on the subjects who developed stroke and collected detailed clinical information throughout the study period. These characteristics of the study design enabled us to examine secular trends in the incidence of and risk factors for ischemic stroke subtypes. We previously reported the steadily increasing incidence of ischemic stroke,17 used follow-up data of the first 3 cohorts.17 In this article, we extend the follow-up period of these cohorts to 13 years and compare the impact of cardiovascular risk factors on the incidence of ischemic stroke subtypes.

Methods

Study Population
The Hisayama Study, an epidemiological study of cerebrovascular-diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town was approximately 8000 in 2007, and full community surveys of the residents have been repeated since 1961. The study design and characteristics of the subject population have been described in detail elsewhere. Briefly, we established 4 study cohorts from Hisayama residents aged 40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. In 1961, a total of 1658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of subjects with a history of stroke or myocardial infarction and subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. Similarly, after excluding subjects with a history of stroke or myocardial infarction, we established a second cohort consisting of 2038 subjects from 2135 participants (participation rate 81.2%) in 1974, a third cohort of 2637 subjects from 2742 participants (participation rate 79.9%) in 1988, and a fourth cohort of 3123 subjects from 3328 participants (participation rate 74.6%) in 1992. The health status of these cohort populations was followed up every year by repeated health examinations or by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up. The development of cardiovascular diseases in the study populations was also checked by a daily monitoring system organized by the study team, local physicians, and members of the local health and welfare office. When the subjects died, autopsy examinations were performed at the Department of Pathology, Kyushu University.

Measurement of Cardiovascular Risk Factors
Details of the measurement of cardiovascular risk factors in each cohort were published previously. In brief, blood pressures were measured 3 times with subjects in a recumbent position in 1961 and in a sitting position in 1974, 1988, and 2002, and hypertension was defined as a mean systolic blood pressure ≥140 mm Hg or a mean diastolic blood pressure ≥90 mm Hg or current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988 and 2002, in addition to medical history of diabetes. Serum cholesterol levels were measured by the Zak-Henly method with the modification by Yoshikawa in 1961, by the Zulkowski method in 1974, and by the enzymatic method in 1988 and 2002. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured with subjects in light clothing without shoes, and obesity was defined as body mass index ≥25.0 kg/m². Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standardized questionnaire and was categorized as current habitual use or not. Current drinking was also categorized as light (1 to 33 g/d) or heavy (≥34 g/d) drinking according to daily ethanol intake.

Definition of Ischemic Stroke Subtypes
Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit that persisted for >24 hours and was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. The diagnoses of ischemic stroke subtypes were made on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke, as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study and Cerebral Embolism Task Force. We classified ischemic stroke subtypes into 4 categories: LAI, atrioventricular infarction (ATI), cardioembolic infarction (CEI), and undetermined subtype. Details of the diagnostic criteria of ischemic stroke subtypes have been published previously.

Briefly, LAI was diagnosed as the presence of a relevant brain stem or subcortical hemorrhagic lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subject had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force. The category of undetermined subtype included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphological information. We considered morphological findings significant and used clinical features as reference information.

During the 13-year follow-up period, first-ever ischemic stroke developed in 134 subjects (83 cases of LAI, 28 of ATI, 17 of CEI, and 6 of undetermined subtype) in the first cohort, in 142 subjects in the second cohort (76 cases of LAI, 29 of ATI, 34 of CEI, and 3 of undetermined subtype), and in 154 subjects in the third cohort (74 cases of LAI, 42 of ATI, 38 of CEI, and 0 of undetermined subtype). Among these, morphological examinations by autopsy or brain imaging were performed on 90.3% (autopsy rate 90.3%) of the first cohort, 97.2% (autopsy rate 87.5%) in the second cohort, and 100.0% (autopsy rate 72.4%) in the third cohort.

Statistical Analysis
The prevalences of possible risk factors were adjusted for age by the direct method and were examined for trends across cohorts by the Cochran-Mantel-Haenszel χ² test with 10-year age groupings. Age-adjusted mean values of risk factors were calculated by the covari-ance method, and their trends were tested by the linear regression model. The incidences of first-ever ischemic stroke and its subtypes were calculated by the person-year method with adjustment for age by the direct method. The world standard population was used as a standard population. The age-adjusted incidences among the first 3 cohorts were compared with the use of the Cox proportional hazards model. Age and sex-adjusted hazard ratios (HRs) and 95% CIs of cardiovascular risk factors for the development of ischemic stroke and its subtypes were estimated by the Cox proportional hazards model in each cohort, and the population attributable risk fraction of each risk factor was calculated.

Ethical Considerations
The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
Hypercholesterolemia was defined as total cholesterol level more than 5.7 mmol/L. Risk factors at baseline examination among the four cohorts by sex (Table 1). During the 40-year period from 1961 to 2002, the populations grew 5 years older in both sexes. The age-adjusted prevalence of hypertension was stable at 11.6% in men and by 40% for women from the first to the third cohort. It significantly declined by 56% for men and by 40% for women from the first to the third cohort through the cohorts: It significantly declined by 56% for men and by 40% for women from the first to the third cohort.

Results
Trends in Cardiovascular Risk Factors
We compared the age-adjusted prevalence of cardiovascular risk factors at baseline examination among the four cohorts by sex (Table 1). During the 40-year period from 1961 to 2002, the populations grew 5 years older in both sexes. The age-adjusted prevalence of hypertension was stable at ~40% in men (P for trend = 0.25) and decreased significantly in women (P for trend < 0.001), whereas the proportion of individuals using antihypertensive agents increased consistently with time in both men and women. As a result, age-adjusted mean blood pressures among hypertensive men and women decreased significantly throughout the study period. In contrast, the age-adjusted prevalence of glucose intolerance and obesity increased greatly over the study period for both sexes. More than half of men and one third of women had glucose intolerance in 2002. The age-adjusted prevalence of hypercholesterolemia increased 10-fold in men and 6-fold in women from 1961 to 1988 but was unchanged in 2002. The age-adjusted prevalence of current smoking for men was 4-fold higher than that for women in 1961, and it decreased significantly with time for both sexes. The prevalence of current drinking increased significantly for both sexes in 2002.

Trends in Incidence of Ischemic Stroke Subtypes
We then compared the age-adjusted incidence of ischemic stroke using the results of a 13-year follow-up in the first 3 cohorts (1st, 2nd, and 3rd cohort). The age-adjusted incidence of ischemic stroke declined significantly for both sexes throughout the cohorts: It significantly declined by 56% for men and by 40% for women from the first to the third cohort (P for trend < 0.001 for either sex; Table 2). In regard to ischemic stroke subtypes, the age-adjusted incidence of LAI for men declined significantly by 54% from the first to the second cohort, and it continued to decline by 39% from the second to the third cohort (P for trend < 0.001). The age-adjusted incidence of LAI for women also declined by 25% from the first to the second cohort, and it continued to decline by 17% from the second to the third cohort (P for trend = 0.003). The age-adjusted incidence of ATI and CEI did not change significantly among the cohorts for either sex.

Trends in Proportion of Ischemic Stroke Subtype
The proportions of ischemic stroke subtypes among the cohorts are shown by sex in the Figure. For men, the proportion of subjects with LAI decreased steadily from the first to the third cohort, whereas the proportions with ATI and CEI increased. For women, the proportion of the subjects with CEI increased slightly from the first to the third cohort, but the proportions of those with the other subtypes were constant among the cohorts.

Trends in the Effect of Cardiovascular Risk Factors on Ischemic Stroke
Because both cardiovascular risk factors and the incidence of ischemic stroke changed dramatically, we compared the impact of cardiovascular risk factors on the development of ischemic stroke among the first 3 cohorts (Table 3). In the first cohort, hypertension was a powerful risk factor for ischemic stroke (age- and sex-adjusted HR 3.25, 95% CI 2.17 to 4.86) and largely contributed to its occurrence (population attributable risk fraction 51%). The impact of hypertension gradually declined during the study period; however, hyper-
tension was still a significant risk factor and made the largest contribution to the development of ischemic stroke even in the third cohort (HR 1.83, 95% CI 1.29 to 2.58, population attributable risk fraction 30%). Glucose intolerance was also a significant risk factor for ischemic stroke in the first cohort. The effect of glucose intolerance on the occurrence of ischemic stroke was reduced and was not significant in the second cohort, but it appeared to be a significant risk factor in the third cohort. The population attributable risk fraction for glucose intolerance decreased from 13% in the first cohort to 4% in the second cohort and then increased to 13% in the third cohort. Obesity appeared to be a significant risk factor for ischemic stroke in every cohort, and its population attributable risk fraction was increased gradually from 6% in the first cohort to 9% in the third cohort. Hypercholesterolemia, smoking habits, and alcohol intake were not significant risk factors for ischemic stroke in any of the cohorts. In the multivariate analysis that included all risk factors, hypertension was a significant risk factor for ischemic stroke, and its HR decreased from 2.92 (95% CI 1.93 to 4.41) in the first cohort to 1.71 (95% CI 1.20 to 2.45) in the third cohort. Glucose intolerance was an independent risk factor for ischemic stroke in the first cohort (HR 1.91, 95% CI 1.23 to 2.95) but was not significant in the third cohort (HR 1.28, 95% CI 0.93 to 1.78). Obesity was not a significant risk factor in any of the cohorts after adjustment for other risk factors. We tried to investigate the effect of cardiovascular risk factors on ischemic stroke subtypes, but we could not find reliable evidence of an effect of these risk factors on the development of each subtype, probably because of the small number of events.

Table 2. Age-Adjusted Incidence Rate (per 1000 Person-Years) of Ischemic Stroke and Its Subtypes Among 3 Cohorts of the Hisayama Study by Sex, With a 13-Year Follow-Up in Each Cohort

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Cohort (7456 PY)</td>
<td>2nd Cohort (9655 PY)</td>
<td>3rd Cohort (12 333 PY)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>72</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>8.73</td>
<td>5.44</td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>LAI</td>
<td>48</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>5.68</td>
<td>2.59</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>ATI</td>
<td>14</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>1.88</td>
<td>1.03</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>CEI</td>
<td>9</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>1.08</td>
<td>1.74</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Undetermined subtype</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Incidence rate</td>
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<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2</td>
<td>0</td>
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</tbody>
</table>

PY indicates person-years.
efforts to improve the treatment of hypertension.

In subjects in the present study, the age-adjusted prevalence of metabolic disorders, such as obesity, hypercholesterolemia, and glucose intolerance, increased greatly during the past 40 years, probably owing to the westernization of the Japanese lifestyle. When we examined the impact of these metabolic disorders on the development of ischemic stroke, glucose intolerance was a significant risk factor in the first and the third cohort, and the impact of obesity was constant throughout the study period. Both glucose intolerance and body mass index have been shown to be significant risk factors for ischemic stroke and LAI. Moreover, obesity is closely related to other cardiovascular risk factors and jointly increases the risk of ischemic stroke.9 Our previous study also showed that the accumulation of metabolic disorders (that is, metabolic syndrome) was a significant risk factor for the development of ischemic stroke in our third cohort.20 We speculate that the improved management of hypertension and the worsening of metabolic disorders cancelled each other out and resulted in the slowdown of the declining trend of the incidence of LAI and the sustained incidence of ATI.

Smoking is a widely accepted risk factor for ischemic stroke in Western populations, but this relationship is controversial for Japanese.10,21,22 In the present study cohorts, the declining prevalence of smoking habits closely mirrored the declining trend in the incidence of ischemic stroke; however, smoking habits had little impact on the incidence of ischemic stroke in the present study cohorts. One possible explanation is that the association between smoking and the risk of ischemic stroke is only evident in populations with moderate to high levels of serum cholesterol.23 A recent review of cardiovascular mortality trends in Japan showed that the increase in serum cholesterol appeared mainly in young to middle-aged people. In contrast, elderly people, a high-risk group for ischemic stroke, continued to maintain a lower cholesterol level. However, the prevalence of smoking habits is still high in Japanese men, and therefore, the adverse influence of smoking might appear in the current generation of younger men, with a higher cholesterol level to be seen in the future.

LAI is the most common subtype of ischemic stroke in the Japanese population, unlike in Western populations.1 Among subjects in the present study, because of the decreased incidence of LAI and the sustained incidences of ATI and CEI, the proportion of ischemic stroke subtypes has become closer to that of Western populations in men (Figure).
However, the pattern of ischemic stroke subtypes differed from that of Western populations, with subjects in the present study showing a high proportion of LAI even in recent years (43% for men and 52% for women in the third cohort). A recent hospital-based registration study in an urban area and a study of 16,992 patients with acute ischemic stroke from rural areas in Japan also showed a higher prevalence of LAI than other subtypes. One possible explanation for this is the racial difference in the genetic susceptibility of LAI. We recently found 2 susceptibility genes for ischemic stroke, PRKCH and AGTR1L, in a genome-wide association study. A single-nucleotide polymorphism in the PRKCH gene increased the risk of LAI, but this single-nucleotide polymorphism is specific to Asian populations.

The present study has several limitations. First, the number of events of subtypes other than LAI was relatively small, and therefore, the power to assess trends in the incidence of and risk factors for ischemic stroke subtypes was weak. Second, there were a large number of subjects overlapping among the cohorts. Indeed, 916 of the subjects in the first cohort also accounted for 45% of the population of the second cohort. In addition, a total of 1,229 subjects in the second cohort also participated in the third cohort (47% of the third cohort). However, we treated the overlapping subjects as in any lifetime table analysis, establishing every cohort after excluding subjects with prior stroke or myocardial infarction at baseline. Therefore, these overlapping populations were not considered to distort the incidence trends in the present study. Third, the measurement of blood glucose and the criteria for glucose intolerance were different among the cohorts, which suggests an underestimation of the prevalence of glucose intolerance in the former cohorts. Nevertheless, the rapid changes in other risk factors in the present study are in accordance with the results of the National Nutritional Survey and other surveys of Japan. Finally, the methods of case ascertainment and the diagnostic sensitivity of imaging techniques changed dramatically during the study period. The proportion of case subjects with of incident ischemic stroke who received diagnostic imaging tests increased over time. Echocardiography and carotid scanning were rarely performed in the former cohorts (3.0% and 0% in the first cohort, 29.6% and 4.2% in the second cohort, and 61.7% and 27.3% in the third cohort, respectively). Therefore, it is possible that the trends in the incidence of ATI and CEI were less accurate than the trends for LAI. Nonetheless, we believe that the findings of the present study reflect the actual secular trends in the incidence of ischemic stroke subtypes and their risk factors in the Japanese population, because we performed comprehensive surveillance, including autopsy examinations, in most of the cases.

Conclusions
By comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the 1960s to the late 1990s, but LAI remained the most frequent subtype of ischemic stroke in the Japanese. The improvement in hypertension control might have had a major influence on this declining trend. However, hypertension still has a large impact on ischemic stroke, and the increasing prevalence of metabolic disorders might emerge as an additional risk in future cohorts. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

Sources of Funding
This study was supported in part by a grant-in-aid for scientific research A (No. 18209024) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosure
None.

References


CLINICAL PERSPECTIVE

Stroke continues to be a major public health concern worldwide. Several epidemiological studies have reported that the declining or stable incidence of stroke is most often attributed to better treatment of risk factors over time. Here, by comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrate that the age-adjusted incidence of ischemic stroke and of lacunar infarction declined significantly from the 1960s to the late 1990s, but lacunar infarction remains the most frequent subtype of ischemic stroke in the Japanese. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. However, hypertension still has a large impact on ischemic stroke, and the increase in metabolic disorders might emerge as an additional risk in the third cohort. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.
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Circulation. 2008;118:2672-2678
doi: 10.1161/CIRCULATIONAHA.107.743211

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