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Long-Term Trends in The 5-Year Risk of Recurrent Stroke over A Half Century in A Japanese Community: The Hisayama Study

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Aim: Secular trends in the risk of recurrent stroke have been reported in several epidemiological studies worldwide, but this issue has not been investigated in general Japanese populations. We examined the trends in the 5-year risk of recurrent stroke over a half century using community-based prospective data in Japan.

Methods: We established 4 cohort studies in 1961, 1974, 1988, and 2002. To examine the risk of recurrent stroke, participants who developed stroke during a 10-year follow-up period in each cohort were followed-up for 5 years from the date of first onset. A total of 154 (first sub-cohort: 1961-1971), 144 (second sub-cohort: 1974-1984), 172 (third sub-cohort: 1988-1998), and 146 (fourth sub-cohort: 2002-2012) participants from each cohort were enrolled in the present study. The 5-year cumulative risk of recurrent stroke was compared among the sub-cohorts using the Kaplan-Meier method and the age- and sex-adjusted Cox proportional hazards model.

Results: The risks of recurrent stroke after any stroke and ischemic stroke decreased significantly from the first to the third sub-cohort, but they did not clearly change from the third to the fourth sub-cohort. The risk of recurrent stroke after hemorrhagic stroke decreased mainly from the first to the second sub-cohort and there was no apparent decrease from the second to the fourth sub-cohort. These trends were substantially unchanged after adjusting for age and sex.

Conclusions: In the Japanese community, the risk of recurrent stroke decreased mainly from the 1960s to 1990s, but there was no apparent decrease in recent years.

Key words: Recurrent stroke, Secular trend, Epidemiology, Japan

Introduction

Stroke is one of the leading cause of death and disability¹⁾. The incidence and mortality rates of stroke have been decreasing over time worldwide²⁾ and in Japan³⁾. However, the national statistical data in Japan reveal that stroke remains the fourth leading cause of death⁴⁾ and the second most common cause of disability with a need for long-term care⁵⁾. In addition, patients with stroke are prone to recurrence⁶⁾, and patients who have recurrent strokes have a higher risk

of death and disability^{7, 8)}. Therefore, recurrence of stroke is an important health issue, and clarification of its secular trends is important for policy planning to reduce the burden of medical and nursing care caused by stroke.

Several observational studies worldwide have examined the secular trends in the risk of recurrent stroke, but their findings have been inconsistent⁹⁻¹⁸⁾. In addition, the secular trends in recurrent stroke were reported to differ among the different geographical regions in the United States¹²⁾. An international

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cohort study of patients with transient ischemic attack or minor stroke reported that the risk of stroke recurrence was significantly higher in Japanese patients than in non-Japanese patients¹⁹). Therefore, the conclusions of previous studies may not be generalized to other populations with different lifestyle, environmental, and genetic backgrounds, and this issue should be discretely examined in each country or community. However, no community-based studies have examined the secular trend in the risk of recurrent stroke in Japan.

In the present study, we examine the secular trends in the 5-year risk of recurrent stroke from the date of first onset using the data from four cohorts covering different time periods, which were established from an epidemiological study for stroke in a Japanese community conducted over a half century. In addition, since the risk of stroke recurrence is considered to be different among the subtypes^{20, 21}), we separately estimated the trends in the risk of stroke recurrence among the subjects with ischemic stroke, among the subjects with hemorrhagic stroke, and among the subjects with each ischemic stroke subtype.

Methods

Availability of Data

The data collected and analyzed in this study are not publicly available due to restrictions included in the informed consent of study participants.

Study Population and Follow-up Surveys

The Hisayama Study is a population-based cohort study of cardiovascular disease that has been ongoing since 1961 in the town of Hisayama, located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. According to the national census, the population of the town was approximately 6500 in 1960 and 9000 in 2020. A detailed description of the Hisayama Study was published previously^{3, 20, 22, 23}). Briefly, annual health examinations for the residents of Hisayama have been conducted by the town government and Kyushu University since 1961. The health examinations conducted in 1961, 1974, 1988, and 2002 were used to establish 4 original cohorts with different time periods. A total of 1658, 2135, 2742, and 3328 residents of Hisayama aged ≥ 40 years participated in the examinations, respectively (participation rate: 78–90% of the total population in this age group). Among them, 1621, 2044, 2646, and 3150 stroke-free participants were included in the first through fourth original cohorts, respectively (Fig. 1).

Each original cohort was followed by the annual

health examinations. Additionally, for participants who did not visit the examination or who moved out of town, health status including new onset of stroke events was checked by mail or telephone interviews. Information on stroke (both first-ever and recurrent events) and death was also collected by a daily monitoring system organized by the study team, local physicians, and the government of Hisayama. When a participant died, autopsy was performed at the Department of Pathology of Kyushu University Hospital if consent for autopsy was obtained by the family members. All available information about potential events of stroke and death among the participants was collected and reviewed by physician members of the study team, including neurologists, to determine the occurrence and classification of stroke and cause of death based on the standardized diagnostic criteria throughout the study period, as described previously²⁴).

In the present study, each original cohort was initially followed up for 10 years for the screening of first-ever stroke events. During the screening periods, first-ever stroke events were recorded for 154, 144, 172, and 146 subjects from the first (1961–1971), second (1974–1984), third (1988–1998), and fourth (2002–2012) cohorts, respectively. These first-ever stroke subjects were included in the sub-cohorts for the present study (the first through the fourth sub-cohorts). Each member of the sub-cohorts was further followed up during the subsequent 5 years from the date of first-ever stroke onset (Fig. 1).

The definitions of risk factors at the baseline health examinations in 1961, 1974, 1988, and 2002 are presented in the Supplemental Methods.

Diagnosis and Classification of Stroke

Stroke was defined as a sudden onset of non-convulsive and focal neurological deficit persisting for over 24 hours or leading to death with no apparent cause other than cerebrovascular origin²⁴). Recurrent stroke was defined as a subsequent stroke event among the subjects with first-ever stroke who had either a new focal neurological deficit or a deterioration of previous deficit that was not caused by cerebral edema, hemorrhagic transformation after first-ever stroke, concomitant disease, or iatrogenesis²⁰). When a deterioration of previous deficit was observed, the case was included as a recurrent stroke event if the symptoms were explained by other vascular territory or if we had clear evidence of new stroke lesions by a repeated computed tomography (CT) or magnetic resonance imaging (MRI). In contrast, it was not included if there was no clear evidence of new stroke lesions.

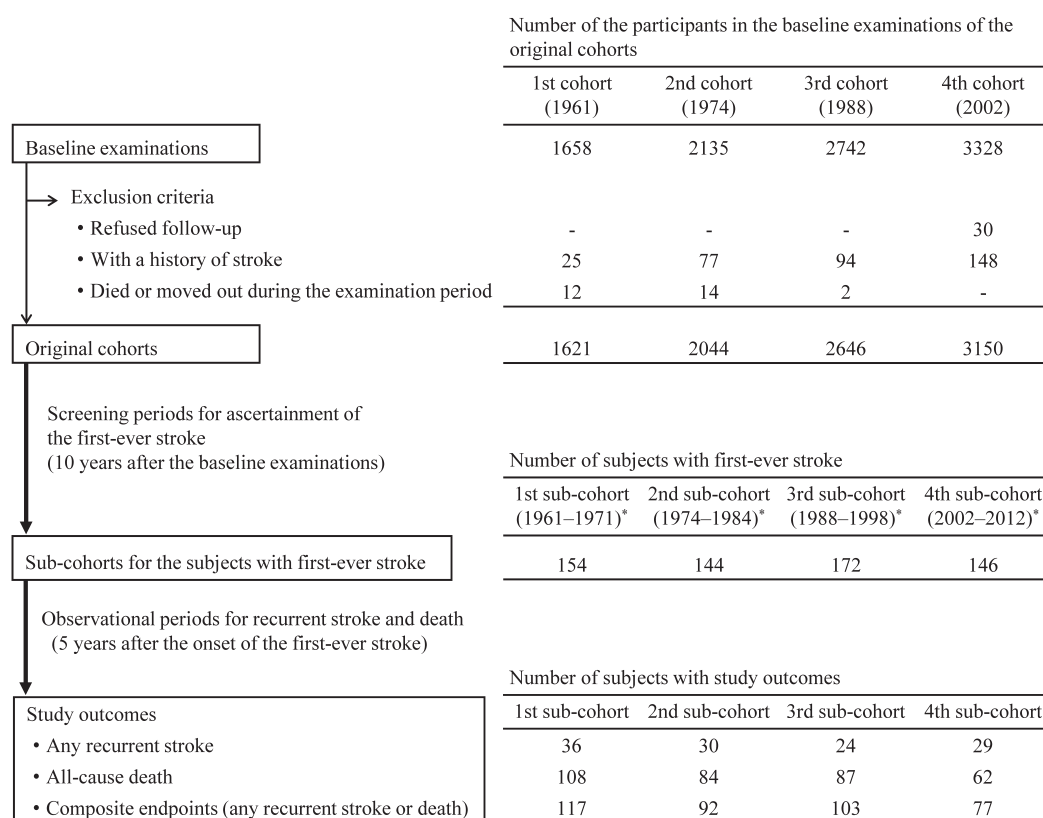


Fig. 1. Flow chart for the study subjects and follow-up surveys

*The periods in parentheses are the 10-year screening period in which the first-ever stroke was enrolled.

First-ever cases of stroke were classified into ischemic, hemorrhagic, or undetermined stroke. Intracerebral hemorrhage and subarachnoid hemorrhage were analyzed together as hemorrhagic stroke because of the small numbers of subjects. Ischemic stroke was further divided into four clinical subtypes: embolic infarction, lacunar infarction, atherothrombotic or other brain infarction, and undetermined infarction²⁴. In the Hisayama Study, cardioembolic infarction and embolic stroke of other/undetermined sources were analyzed together as “embolic infarction,” because information about embolic sources was often unavailable, especially in the earlier cohorts. Lacunar infarction was defined as ischemic stroke caused by an infarct lesion with a diameter of <1.5 cm in deep brain regions (the subcortical hemispheric area or brainstem) without evidence of cerebral cortical or cerebellar dysfunction. Atherothrombotic or other brain infarction included atherothrombotic brain infarction, characterized by cerebral cortical or cerebellar infarction caused by the stenosis or occlusion of a carotid or major cerebral artery or its branch, and other non-embolic non-lacunar infarction. Ischemic strokes in deep brain regions with a diameter >1.5 cm and ischemic strokes

caused by artery-to-artery or aortogenic embolism were included in this category. Undetermined infarction included ischemic stroke cases for which the subtype cannot be determined because of insufficient information. The diagnosis and classification of stroke were based on all available clinical information, including medical interview, physical examination, hospital records, brain imaging such as CT or MRI, and autopsy findings. Morphological evaluation of the brain (brain CT, MRI, or autopsy) was performed on 95% of the stroke subjects in the present study.

Study Outcomes

The primary outcome of the present study was any recurrent stroke (either ischemic or hemorrhagic) over the 5 years after the onset of first-ever stroke. Only the first recurrent stroke events were analyzed. During the 5-year observational periods, 36, 30, 24, and 29 subjects had recurrent stroke from the first through the fourth sub-cohorts, respectively. The secondary outcomes were all-cause mortality and composite endpoints (any recurrent stroke and all-cause mortality) during the same periods. During the 5-year observational periods, 108, 84, 87, and 62 subjects died, and 117, 92, 103, and 77 subjects

Table 1. Baseline characteristics of the study subjects with first-ever stroke in each sub-cohort of the Hisayama Study

Sub-cohort (onset year of first-ever stroke)	1st sub-cohort (1961–1971)	2nd sub-cohort (1974–1984)	3rd sub-cohort (1988–1998)	4th sub-cohort (2002–2012)	<i>P</i> for trend
Number of subjects with first-ever stroke	154	144	172	146	
Age at first-ever stroke (year), mean (SD)	69.1 (10.1)	73.5 (10.0)	73.5 (11.6)	75.4 (11.7)	<0.001
Men, <i>n</i> (%)	86 (56)	64 (44)	73 (42)	73 (50)	0.24
Type of first-ever stroke, <i>n</i> (%)					
Ischemic stroke	106 (69)	108 (75)	119 (69)	100 (68)	0.70
Embolic infarction*	11 (10)	27 (25)	28 (24)	30 (30)	0.002
Lacunar infarction*	68 (64)	57 (53)	60 (50)	37 (37)	<0.001
Atherothrombotic or other brain infarction*	22 (21)	22 (20)	31 (26)	26 (26)	0.24
Undetermined brain infarction*	5 (5)	2 (2)	0 (0)	7 (7)	0.60
Hemorrhagic stroke	44 (29)	36 (25)	53 (31)	45 (31)	0.45
Brain hemorrhage	30 (19)	23 (16)	35 (20)	29 (20)	0.70
Subarachnoid hemorrhage	14 (9)	13 (9)	18 (10)	16 (11)	0.52
Undetermined stroke	4 (3)	0 (0)	0 (0)	1 (1)	0.10
Morphological evaluation, <i>n</i> (%)	130 (84)	140 (97)	172 (100)	145 (99)	<0.001
Brain imaging (CT or MRI)	7 (5)	88 (61)	167 (97)	142 (97)	<0.001
Brain autopsy	130 (84)	124 (86)	114 (66)	58 (40)	<0.001

Abbreviations: SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

*The percentage indicates the proportion of each subtype among the subjects with ischemic stroke.

experienced composite endpoints (Fig. 1). No subjects in any of the sub-cohorts were lost to follow-up over the 5 years after the first-ever stroke.

Statistical Analysis

The secular trend in mean age at onset of first-ever stroke was tested using a general linear regression model. The secular trends in the proportion of men, each pathological type of first-ever stroke, and each clinical subtype of first-ever ischemic stroke were tested using logistic regression models. The secular trends in risk factors at baseline examinations were tested using linear regression for continuous variables and logistic regression for binominal variables. The crude cumulative rates of the study outcomes were estimated by the Kaplan-Meier method and their secular trends were tested by a univariate Cox proportional hazards model. The age- and sex-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the study outcomes among the sub-cohorts were estimated by a Cox proportional hazards model in which the first sub-cohort was used as a reference group. The age- and sex-adjusted subdistribution HRs (95% CI) considering all-cause mortality as a competing event were estimated using the Fine and Gray model²⁵. All analyses were performed using SAS software package version 9.4 (SAS Institute). Two-sided *P* values <0.05 were considered statistically significant in all analyses.

Ethical Considerations

The protocol of the Hisayama Study was approved by the Kyushu University Institutional Review Board for Clinical Research. Oral informed consent was obtained from the participants of the first through the third cohorts, and written informed consent was obtained from the participants of the fourth cohort.

Results

The demographic characteristics of the study subjects with first-ever stroke in each sub-cohort are summarized in Table 1. Mean age at onset of first-ever stroke became significantly older with time. Although the proportion of ischemic stroke among total stroke was not substantially different among the sub-cohorts, the proportion of each subtype of ischemic stroke clearly changed with time. While the proportion of embolic infarction among the total ischemic stroke group increased significantly with time, the proportion of lacunar infarction decreased significantly.

Information on risk factors at the baseline health examination of each sub-cohort (i.e., the health examinations in 1961, 1974, 1988, and 2002) are presented in Supplemental Table 1. The prevalence of hypertension and mean values of systolic and diastolic blood pressure decreased significantly, and the proportion of subjects using antihypertensive

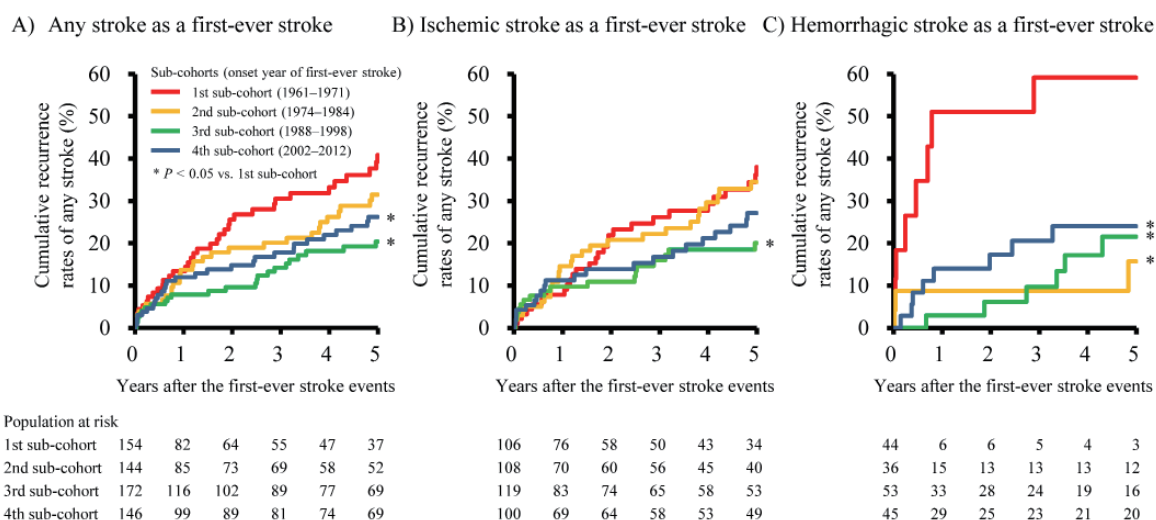


Fig. 2. Kaplan-Meier estimates of any recurrent stroke after any stroke as a first-ever stroke (A), ischemic stroke as a first-ever stroke (B), and hemorrhagic stroke as a first-ever stroke (C)

* $P < 0.05$ compared with the first sub-cohort tested using a univariate Cox proportional hazards model.

agents increased significantly from the first to the fourth sub-cohort. On the other hand, the prevalence of glucose intolerance and hypercholesterolemia increased significantly with time, and the prevalence of obesity and atrial fibrillation showed non-significant upward trends. The proportion of current smokers decreased significantly with time, and the proportion of current drinkers showed a non-significant downward trend.

Fig. 2 shows the secular trends in the crude cumulative recurrence rates of any stroke determined using the Kaplan-Meier method. Among the subjects with any first-ever stroke, the 5-year cumulative recurrence rates of any stroke gradually decreased from the first to the third sub-cohort, but there was no significant change from the third to the fourth sub-cohort ($P = 0.28$). With regard to the subtype of first-ever stroke, the cumulative recurrence rates of any stroke showed a similar pattern in subjects whose first-ever stroke was ischemic. In contrast, the cumulative recurrence rates of any stroke declined sharply from the first to the second sub-cohort, and then remained stable from the second to the fourth sub-cohort in those whose first-ever stroke was hemorrhagic. **Table 2** shows the age- and sex-adjusted HRs for recurrent stroke among the sub-cohorts. The patterns of secular changes in the risk of recurrent stroke were essentially unchanged after adjusting for age and sex: the risk of recurrent stroke decreased mainly from the first to the third sub-cohort for any first-ever stroke and ischemic stroke, and from the first to the second sub-cohort for hemorrhagic stroke. Similar patterns were observed even after excluding the subjects who had recurrent

stroke or death within 30 days after the first-ever stroke as a sensitivity analysis (**Supplemental Fig. 1 and Supplemental Table 2**). We performed another sensitivity analysis considering the competing risk of death using the Fine and Gray model (**Supplemental Table 3**). The reduction in the risk of stroke recurrence between the first to the third sub-cohorts remained significant among the subjects with any stroke or those whose first-ever stroke was ischemic.

Table 3 shows the secular trend in the age- and sex-adjusted risk of recurrent stroke among the subjects with each subtype of ischemic stroke. The risk of any recurrent stroke decreased mainly from the second to the third sub-cohort among the subjects with embolic infarction, and declined mainly from the first to the second sub-cohort among the subjects with lacunar infarction. On the other hand, there was no apparent decline in the risk of recurrent stroke among the subjects with atherothrombotic or other brain infarction.

The secular trends in the 5-year risk of all-cause mortality are demonstrated in **Supplemental Table 4**. Among the subjects with any first-ever stroke, the 5-year risk of all-cause mortality showed a consistent downward trend from the first to the fourth sub-cohort. A similar decreasing pattern was observed in both subjects whose first-ever stroke was ischemic and those whose first-ever stroke was hemorrhagic. Similarly, the risk of the composite endpoints (any recurrent stroke and all-cause mortality) showed a consistent descending trend over time (**Supplemental Table 5**).

Finally, the type of the recurrent stroke was

Table 2. Secular trends in the crude cumulative risks and age- and sex-adjusted hazard ratios for any recurrent stroke according to the types of first-ever stroke

Type of first-ever stroke	Number of events with any recurrent stroke	Crude 5-year cumulative recurrence rate (%)	Age- and sex-adjusted	
			HR (95%CI)	P value
Any stroke				
1st sub-cohort (n=154)	36	40.8	1.00 (reference)	
2nd sub-cohort (n=144)	30	31.5	0.67 (0.41–1.09)	0.11
3rd sub-cohort (n=172)	24	20.4	0.38 (0.23–0.65)	<0.001
4th sub-cohort (n=146)	29	26.2	0.50 (0.30–0.82)	0.006
P for trend				0.002
Ischemic stroke				
1st sub-cohort (n=106)	28	38.0	1.00 (reference)	
2nd sub-cohort (n=108)	27	34.5	0.82 (0.48–1.39)	0.46
3rd sub-cohort (n=119)	18	20.0	0.43 (0.24–0.79)	0.007
4th sub-cohort (n=100)	21	27.1	0.57 (0.32–1.01)	0.06
P for trend				0.01
Hemorrhagic stroke				
1st sub-cohort (n=44)	8	59.2	1.00 (reference)	
2nd sub-cohort (n=36)	3	15.8	0.19 (0.05–0.72)	0.01
3rd sub-cohort (n=53)	6	21.5	0.17 (0.05–0.50)	0.001
4th sub-cohort (n=45)	8	24.0	0.22 (0.08–0.63)	0.004
P for trend				0.02

Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 3. Secular trends in the crude cumulative risks and age- and sex-adjusted hazard ratios for any recurrent stroke according to the subtypes of ischemic stroke

Type of first-ever stroke	Number of events with any recurrent stroke	Crude 5-year cumulative recurrence rate (%)	Age- and sex-adjusted	
			HR (95%CI)	P value
Embolic infarction				
1st sub-cohort (n=11)	2	35.7	1.00 (reference)	
2nd sub-cohort (n=27)	10	57.2	1.18 (0.24–5.85)	0.84
3rd sub-cohort (n=28)	0	0.0	0.00	0.99
4th sub-cohort (n=30)	3	15.9	0.16 (0.02–1.26)	0.08
P for trend				0.005
Lacunar infarction				
1st sub-cohort (n=68)	21	39.4	1.00 (reference)	
2nd sub-cohort (n=57)	10	22.5	0.51 (0.24–1.09)	0.08
3rd sub-cohort (n=60)	11	21.1	0.40 (0.19–0.86)	0.02
4th sub-cohort (n=37)	8	24.2	0.43 (0.19–1.00)	0.049
P for trend				0.02
Atherothrombotic or other brain infarction				
1st sub-cohort (n=22)	5	41.1	1.00 (reference)	
2nd sub-cohort (n=22)	6	42.1	0.72 (0.21–2.42)	0.60
3rd sub-cohort (n=31)	7	27.4	0.70 (0.22–2.27)	0.56
4th sub-cohort (n=26)	9	39.2	0.87 (0.28–2.66)	0.81
P for trend				0.92

Abbreviations: HR, hazard ratio; CI, confidence interval.

compared with that of the first-ever stroke in [Supplemental Table 6](#). Among most of the subjects with ischemic stroke as a first-ever event, the type of the recurrent event was also ischemic stroke in all sub-cohorts (86–96%). Among the subjects with hemorrhagic stroke as a first-ever event, the most common type of the recurrent events was also hemorrhagic in the first three sub-cohorts (67–88%). However, in the fourth sub-cohort, ischemic stroke (63%) was a more common recurrent type than hemorrhagic stroke (38%).

Discussion

Using the community-based prospective data of Japanese subjects with first-ever stroke, we examined the long-term trends in the 5-year risk of recurrent stroke among 4 sub-cohorts with different time periods. The 5-year risks of recurrent stroke after any stroke or ischemic stroke decreased mainly from the first sub-cohort (onset year of first-ever stroke: 1961–1971) to the third sub-cohort (1988–1998), but did not exhibit any clear pattern of decrease from the third sub-cohort to the fourth sub-cohort (2002–2012). The risk of recurrent stroke after hemorrhagic stroke decreased mainly from the first sub-cohort to the second sub-cohort (1974–1984), and there was no apparent decrease in the risk of recurrent stroke in the more recent sub-cohorts. These findings may provide important information for policy making to prevent recurrent stroke to reduce the burden of medical and nursing care associated with stroke.

Several reports have examined the secular trends in the risk of recurrence after stroke, but their results were inconsistent. While some reports showed that the risk of recurrent stroke decreased with time^{10–14, 16, 17}, others showed that the risk of recurrent stroke was unchanged⁹ or increased^{15, 18}. The reason for the inconsistent findings among the previous reports is unclear but may be related to regional differences (i.e., the prevalence of stroke and its risk factors, proportion of stroke subtypes, availability of treatment and diagnostic procedures, and lifestyle, environmental, and genetic factors), and/or to differences in the methods used to assess first-ever and recurrent stroke events among studies. Moreover, most of the previous reports have examined relatively recent trends in the risk of recurrent stroke (the 1980s or later), and none have reviewed long-term trends in the risk of recurrent stroke over more than half a century in the general population of the same region. To the best of our knowledge, the present study is the first report to examine the secular trends in the risk of recurrent stroke in a single Japanese community. This study

included a very long overall study period (more than half a century, from the 1960s to the 2010s).

In the present study, the risk of recurrent stroke after first-ever stroke decreased mainly in the earlier sub-cohorts (from the first to the third sub-cohort). This finding can be attributed to the improvement of diagnostic neuroimaging techniques such as CT and MRI and advances in treatment for stroke and its risk factors during the past half century, which have enabled us to diagnose and classify the subtypes of stroke accurately, to treat subjects appropriately according to their conditions, and to manage risk factors from the acute to the chronic phase of stroke for prevention of recurrent stroke^{26–28}. However, a clear reduction in the risk of recurrent stroke was no longer observed in the recent sub-cohorts. The reason for this finding is not clear, but several possibilities can be considered. First, the increase in metabolic disorders such as glucose intolerance and hypercholesterolemia may have contributed to the results. Such metabolic disorders are known to cause atherosclerosis in large vessels, which is the etiology of atherothrombotic stroke²⁹. As shown in [Table 3](#), there was no obvious reduction in the risk of recurrent stroke after atherothrombotic or other brain infarction over the entire study period in spite of the improvement in medical care. These findings indicate that comprehensive evaluation and management of atherothrombotic brain infarction, its risk factors, and underlying atherosclerotic lesions in intracranial and extracranial arteries are necessary to reduce the risk of recurrent stroke in the future. Second, as shown in [Supplemental Table 4](#), the risk of death after first-ever stroke decreased consistently throughout the overall study period, probably due to advances in medical care in the acute and chronic phases of stroke and its comorbid diseases. This may have led to an increase in the proportion of survivors with severe stroke who are likely to be at higher risk of recurrent stroke, resulting in no clear reduction in stroke recurrence in the recent sub-cohort. Unfortunately, this hypothesis could not be evaluated because we do not have data on severity and treatment of stroke and its comorbidities. In addition, no clear reduction in stroke recurrence between the third and the fourth sub-cohorts was observed even in the sensitivity analysis considering the competing risk of death. Therefore, the influence of mortality on stroke recurrence remained unclear.

In the present study, among the subjects with hemorrhagic stroke as a first-ever event, the proportion of hemorrhagic stroke as a recurrent event decreased with time, probably due to an improvement in hypertension management. However, the

proportion of ischemic stroke as a recurrent event after hemorrhagic stroke tended to increase in the fourth sub-cohort, probably due to the increases in risk factors other than hypertension (i.e., glucose intolerance, hypercholesterolemia, obesity, and atrial fibrillation). These findings suggest that comprehensive evaluation and management of these risk factors is necessary to reduce the burden of stroke recurrence among the subjects with hemorrhagic stroke in the future.

In regard to the strengths of the present study, this is the only observational cohort study employing stroke recurrence data collected over more than half a century in a single Japanese community. The participation rate in the baseline examination of each original cohort was relatively high (78–90%), and we were able to follow up all the subjects with first-ever stroke for 5 years: no subjects were lost. In addition, we consider that our comprehensive follow-up system, which included annual health examinations, detailed questionnaires, data collection from the clinics/hospitals, and autopsy, enabled us to collect stroke events (both first-ever and recurrent cases) more exhaustively than large-scale registry-based studies. In registry-based studies of stroke, cases of minor stroke without hospitalization or fatal stroke resulting in sudden death could be underreported. Moreover, our comprehensive surveys enabled us to diagnose, adjudicate, and classify stroke events more accurately by a panel discussion including stroke neurologists²⁴. Thus, the findings from the present study can provide relatively accurate information on the long-term prognosis of stroke in this community. The study also had some limitations. First, because this study was not hospital-based, we did not have sufficient information regarding severity of stroke and treatment for stroke or its risk factors during the acute and chronic phases of stroke. Therefore, it was difficult to evaluate the exact reasons for the secular changes in the risk of recurrent stroke. Second, the proportion of stroke diagnosed by neurological imaging modalities such as CT and MRI increased significantly with time (Table 1), which may have affected the detection of stroke recurrence. When neurological imaging was unavailable, a recurrent stroke event was diagnosed by neurological symptoms and autopsy findings (if available) only. Therefore, the recurrent rates of stroke reported in the present study might have been underestimated mainly in the earlier sub-cohorts. However, we consider that such an information bias would not have substantially affected the main study conclusion that the greatest decrease in stroke recurrence was observed from the first to the third sub-cohorts. Third, the lack of a clear reduction in stroke recurrence in recent sub-cohorts may have

been merely due to the play of chance, since there were relatively small numbers of recurrent stroke events. The recent trend in stroke recurrence needs to be reevaluated using a new sub-cohort of the Hisayama study (i.e., “the fifth sub-cohort” based on the health examination in 2017) or examined by other large-scale observational studies. Finally, the present study was conducted in a single community in Japan where a comprehensive health examination with high participation rates has been repeated over the past 60 years. For this reason, the risk factors of the residents of Hisayama may have been more treated or controlled than those of other Japanese communities. Therefore, we need to consider the generalizability of the present study results to other Japanese communities carefully.

Conclusion

The risk of recurrent stroke decreased mainly from the 1960s to the 1990s, but there has been no apparent change in recent years in the general Japanese community. Comprehensive evaluation and management of risk factors, and underlying vascular lesions and embolic sources are needed to reduce the risk of recurrent stroke in the future. In recent years, there have been remarkable advances in thrombolytic therapy, endovascular therapy, antithrombotic agents, treatment of risk factors, and evidence-based clinical guidelines for stroke. We need to continue the observational study of recurrent stroke to examine the impact of recent advances in stroke management on stroke prognosis in the future.

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Conflicts of Interest

We have no conflict of interest to declare.

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SUPPLEMENTAL MATERIAL

Long-term trends in the 5-year risk of recurrent stroke over a half century in a Japanese community: the Hisayama Study

Supplemental Methods

Definition of Risk Factors

Information on risk factors was collected at health examinations in 1961, 1974, 1988, and 2002 (not at onset of stroke), respectively.

Blood pressure was measured three times in a supine position in 1961 and in a seated position in 1974, 1988, and 2002. The mean of three measurements was used in the present study. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive agents.

Glucose intolerance was defined by oral glucose tolerance test in participants with glycosuria in 1961 and by fasting or postprandial plasma glucose concentrations in 1974. The detailed definitions of glucose intolerance in 1961 and 1974 were described

previously¹⁾. In 1988 and 2002, we performed a 75-g OGTT for most of the participants, and glucose intolerance was defined as a fasting plasma glucose concentration ≥ 110 mg/dL, 2-h postload plasma glucose concentration ≥ 140 mg/dL, postprandial plasma glucose concentration ≥ 200 mg/dL, or use of antidiabetic agents.

Hypercholesterolemia was defined as serum total cholesterol ≥ 220 mg/dL and/or use of lipid-modifying agents (information on lipid-modifying agents was available only in 2002). Obesity was defined as body mass index ≥ 25 kg/m². Atrial fibrillation was diagnosed by the Minnesota code classification system on an electrocardiogram at health examination. Smoking and drinking habits were categorized as either current use or not.

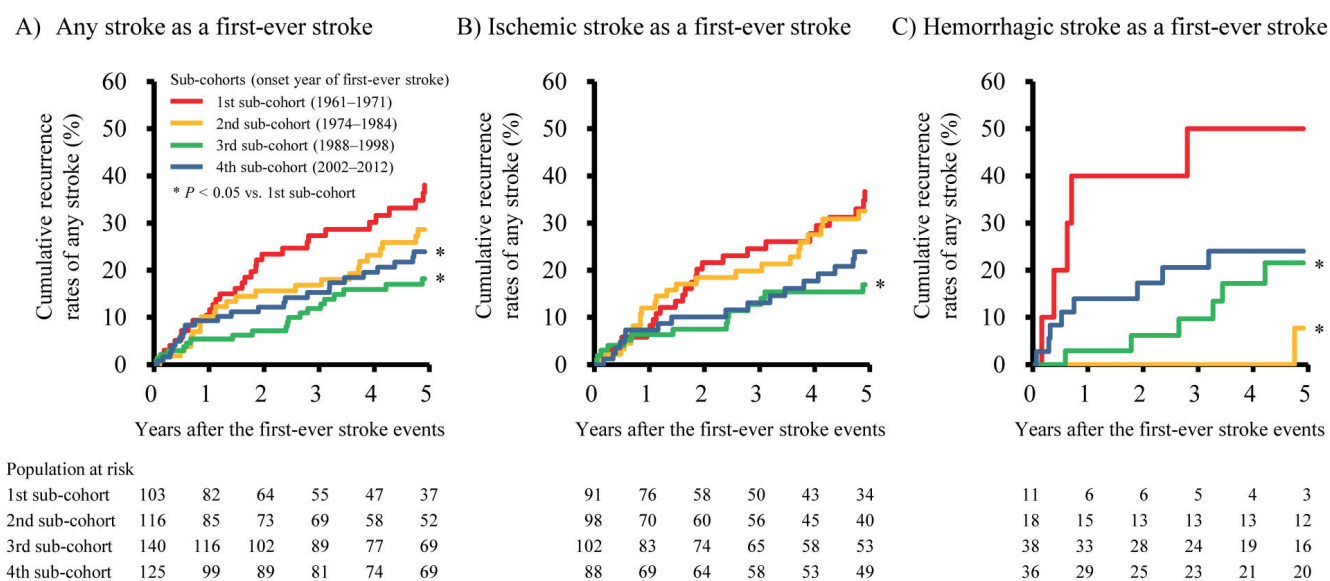
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Supplemental Table 1. Mean values or proportions of risk factors at the baseline health examinations among the subjects with first-ever stroke in each sub-cohort

Sub-cohort (year of screen examination)	1st sub-cohort (1961)	2nd sub-cohort (1974)	3rd sub-cohort (1988)	4th sub-cohort (2002)	<i>P</i> for trend
Number of subjects with first-ever stroke	154	144	172	146	
Age at the baseline examination (year), mean (SD)	64.7 (10.3)	67.8 (10.5)	68.4 (11.8)	70.9 (11.9)	<0.001
Hypertension, <i>n</i> (%)	119 (77)	112 (78)	125 (73)	92 (63)	0.004
Systolic blood pressure (mmHg), mean (SD)	158.5 (28.2)	157.3 (29.6)	149.5 (23.2)	142.0 (24.3)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	89.0 (15.0)	85.9 (14.2)	80.9 (13.2)	81.4 (15.8)	<0.001
Use of antihypertensive agents, <i>n</i> (%)	8 (5)	28 (19)	49 (28)	46 (32)	<0.001
Glucose intolerance, <i>n</i> (%)	28 (18)	22 (15)	73 (42)	81 (55)	<0.001
Hypercholesterolemia, <i>n</i> (%)	10 (6)	32 (22)	57 (33)	54 (37)	<0.001
Serum total cholesterol (mg/dL), mean (SD)	159.9 (39.0)	193.3 (42.2)	202.9 (40.5)	203.2 (38.1)	<0.001
Use of lipid-modifying agents, <i>n</i> (%)	-	-	-	15 (10)	-
Obesity, <i>n</i> (%)	17 (11)	30 (21)	42 (24)	27 (18)	0.06
Body mass index (kg/m ²), mean (SD)	21.7 (2.9)	22.2 (3.6)	22.6 (3.3)	22.1 (3.4)	0.14
Atrial fibrillation on electrocardiogram, <i>n</i> (%)	3 (2)	7 (5)	5 (3)	10 (7)	0.09
Current smoking, <i>n</i> (%)	74 (50)	54 (38)	50 (29)	33 (23)	<0.001
Current drinking, <i>n</i> (%)	66 (45)	51 (35)	48 (28)	55 (38)	0.08

Abbreviation: SD, standard deviation.

The risk factor profiles were obtained at the baseline health examinations (in 1961, 1974, 1988, and 2002), not at the onset of stroke. The definitions of the risk factors are described in the Supplemental Methods. The information on lipid-modifying agents was available only in 2002.

**Supplemental Fig. 1.** Kaplan-Meier estimates of any recurrent stroke after any stroke as a first-ever stroke (A), after ischemic stroke as a first- ever stroke (B), and after hemorrhagic stroke as a first-ever stroke (C): a sensitivity analysis excluding the subjects who had died or experienced recurrent stroke within 30 days

Supplemental Table 2. Secular trends in the crude cumulative risks and age- and sex-adjusted hazard ratios for any recurrent stroke according to the types of first-ever stroke: a sensitivity analysis excluding the subjects who had died or experienced recurrent stroke within 30 days

Type of first-ever stroke	Number of events with any recurrent stroke	Crude 5-year cumulative recurrence rate (%)	Age- and sex-adjusted	
			HR (95%CI)	P value
Any stroke				
1st sub-cohort (n=103)	31	38.1	1.00 (reference)	
2nd sub-cohort (n=116)	25	28.6	0.64 (0.38–1.09)	0.10
3rd sub-cohort (n=140)	20	18.2	0.35 (0.20–0.62)	<0.001
4th sub-cohort (n=125)	25	23.9	0.47 (0.28–0.81)	0.007
P for trend				0.002
Ischemic stroke				
1st sub-cohort (n=91)	26	36.7	1.00 (reference)	
2nd sub-cohort (n=98)	24	32.5	0.77 (0.44–1.35)	0.36
3rd sub-cohort (n=102)	14	17.0	0.34 (0.18–0.66)	0.001
4th sub-cohort (n=88)	17	23.9	0.47 (0.25–0.88)	0.02
P for trend				0.003
Hemorrhagic stroke				
1st sub-cohort (n=11)	5	50.0	1.00 (reference)	
2nd sub-cohort (n=18)	1	7.7	0.10 (0.01–0.86)	0.04
3rd sub-cohort (n=38)	6	21.5	0.25 (0.07–0.85)	0.03
4th sub-cohort (n=36)	8	24.0	0.32 (0.10–1.04)	0.06
P for trend				0.30

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Table 3. Age- and sex-adjusted subdistribution hazard ratios for any recurrent stroke according to the types of first-ever stroke considering a competing risk of death using the Fine and Gray model

Type of first-ever stroke	Number of events with any recurrent stroke	Number of deaths as a competing event*	Age- and sex-adjusted	
			sHR (95%CI)	P value
Any stroke				
1st sub-cohort (n=154)	36	81	1.00 (reference)	
2nd sub-cohort (n=144)	30	62	0.82 (0.51–1.34)	0.44
3rd sub-cohort (n=172)	24	79	0.54 (0.32–0.91)	0.02
4th sub-cohort (n=146)	29	48	0.74 (0.45–1.23)	0.25
P for trend				0.12
Ischemic stroke				
1st sub-cohort (n=106)	28	44	1.00 (reference)	
2nd sub-cohort (n=108)	27	41	0.91 (0.54–1.53)	0.71
3rd sub-cohort (n=119)	18	48	0.53 (0.29–0.97)	0.04
4th sub-cohort (n=100)	21	30	0.72 (0.40–1.27)	0.25
P for trend				0.10
Hemorrhagic stroke				
1st sub-cohort (n=44)	8	33	1.00 (reference)	
2nd sub-cohort (n=36)	3	21	0.39 (0.10–1.49)	0.17
3rd sub-cohort (n=53)	6	31	0.52 (0.17–1.54)	0.24
4th sub-cohort (n=45)	8	17	0.83 (0.30–2.34)	0.73
P for trend				0.87

Abbreviations: sHR, subdistribution hazard ratio; CI, confidence interval.

*The number of subjects who died without stroke recurrence within 5 years.

Supplemental Table 4. Secular trends in the crude cumulative risks and age- and sex-adjusted hazard ratios for all-cause mortality according to the types of first-ever stroke

Type of first-ever stroke	Number of deaths	Crude 5-year cumulative mortality rate (%)	Age- and sex-adjusted	
			HR (95%CI)	P value
Any stroke				
1st sub-cohort (n=154)	108	70.1	1.00 (reference)	
2nd sub-cohort (n=144)	84	58.3	0.62 (0.46–0.82)	<0.001
3rd sub-cohort (n=172)	87	50.6	0.44 (0.33–0.59)	<0.001
4th sub-cohort (n=146)	62	42.5	0.33 (0.24–0.46)	<0.001
P for trend				<0.001
Ischemic stroke				
1st sub-cohort (n=106)	65	61.3	1.00 (reference)	
2nd sub-cohort (n=108)	60	55.6	0.70 (0.49–1.00)	0.049
3rd sub-cohort (n=119)	55	46.2	0.47 (0.32–0.68)	<0.001
4th sub-cohort (n=100)	40	40.0	0.35 (0.23–0.53)	<0.001
P for trend				<0.001
Hemorrhagic stroke				
1st sub-cohort (n=44)	39	88.6	1.00 (reference)	
2nd sub-cohort (n=36)	24	66.7	0.42 (0.25–0.72)	0.001
3rd sub-cohort (n=53)	32	60.4	0.25 (0.15–0.42)	<0.001
4th sub-cohort (n=45)	21	46.7	0.17 (0.10–0.30)	<0.001
P for trend				<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Table 5. Secular trends in the crude cumulative risks and age- and sex-adjusted hazard ratios for composite endpoints (any recurrent stroke and all-cause mortality) according to the types of first-ever stroke

Type of first-ever stroke	Number of events with composite endpoints	Crude 5-year cumulative risk of composite endpoints (%)	Age- and sex-adjusted	
			HR (95%CI)	P value
Any stroke				
1st sub-cohort (n=154)	117	76.0	1.00 (reference)	
2nd sub-cohort (n=144)	92	63.9	0.62 (0.47–0.81)	<0.001
3rd sub-cohort (n=172)	103	59.9	0.50 (0.38–0.66)	<0.001
4th sub-cohort (n=146)	77	52.7	0.40 (0.30–0.54)	<0.001
P for trend				<0.001
Ischemic stroke				
1st sub-cohort (n=106)	72	67.9	1.00 (reference)	
2nd sub-cohort (n=108)	68	63.0	0.72 (0.51–1.01)	0.06
3rd sub-cohort (n=119)	66	55.5	0.55 (0.39–0.77)	<0.001
4th sub-cohort (n=100)	51	51.0	0.45 (0.31–0.66)	<0.001
P for trend				<0.001
Hemorrhagic stroke				
1st sub-cohort (n=44)	41	93.2	1.00 (reference)	
2nd sub-cohort (n=36)	24	66.7	0.38 (0.23–0.65)	<0.001
3rd sub-cohort (n=53)	37	69.8	0.28 (0.17–0.45)	<0.001
4th sub-cohort (n=45)	25	55.6	0.20 (0.12–0.34)	<0.001
P for trend				<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Table 6. The association of the first-ever stroke type and the recurrent stroke type in each sub-cohort

Type of first-ever stroke	Number of subjects with first-ever stroke	Number of events with recurrent stroke			
		Total	Ischemic	Hemorrhagic	Undetermined
1st sub-cohort					
Ischemic stroke	106	28	24 (86%)	4 (14%)	0 (0%)
Hemorrhagic stroke	44	8	1 (13%)	7 (88%)	0 (0%)
Undetermined stroke	4	0	0	0	0
2nd sub-cohort					
Ischemic stroke	108	27	26 (96%)	1 (4%)	0 (0%)
Hemorrhagic stroke	36	3	1 (33%)	2 (67%)	0 (0%)
Undetermined stroke	0	0	0	0	0
3rd sub-cohort					
Ischemic stroke	119	18	16 (89%)	2 (11%)	0 (0%)
Hemorrhagic stroke	53	6	2 (33%)	4 (67%)	0 (0%)
Undetermined stroke	0	0	0	0	0
4th sub-cohort					
Ischemic stroke	100	21	19 (90%)	2 (10%)	0 (0%)
Hemorrhagic stroke	45	8	5 (63%)	3 (38%)	0 (0%)
Undetermined stroke	1	0	0	0	0

Percentages in parentheses indicate the proportion of recurrent stroke type among the subjects with recurrent stroke.