Table S6). Among them, NEUROD6 is known to be involved in the regulation of neuronal fate in the mammalian retina (Kay et al. 2011) and SATB1 has been shown to play a role during postnatal brain development (Balamotis et al. 2012) as well as in aging, dietary restriction, and insulin-like signaling (Zhang et al. 2009). Expression of the *NEUROD6* gene has been shown to be induced by SATB2 (Kay et al. 2011), suggesting that SATB1 may be involved in regulation of *NEUROD6* in adult brain, because SATB1 and SATB2 share some targets and cooperatively regulate their expression (Asanoma et al. 2012). NEUROD6 is a basic helix-loop-helix transcription factor that plays important roles in the mammalian central nervous system including the retina (Kay et al. 2011), and has been shown to confer tolerance to oxidative stress by triggering an antioxidant response and sustaining mitochondrial biomass (Uittenbogaard et al. 2010). Thus, downregulation of *NEUROD6* in AD brain may also accelerate neurodegeneration.

Conclusion

The findings of the present study clearly show that expression of genes involved in insulin signaling related to DM is significantly diminished, likely as a result of AD pathology, even in the absence of peripheral DM-related abnormalities. These findings provide new insights into the molecular mechanisms underlying AD pathology and will help us to develop new strategies for the prevention of and therapy for AD.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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Secular Trends in Cardiovascular Disease and Its Risk Factors in Japanese

Half-Century Data From the Hisayama Study (1961–2009)

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Background—Changes in lifestyle and advances in medical technology during the past half century are likely to have affected the incidence and mortality of cardiovascular disease and the prevalence of its risk factors in Japan.

Methods and Results—We established 5 cohorts consisting of residents aged ≥40 years in a Japanese community, in 1961 (n=1618), 1974 (n=2038), 1983 (n=2459), 1993 (n=1983), and 2002 (n=3108), and followed up each cohort for 7 years. The age-adjusted incidence of stroke decreased greatly, by 51% in men and by 43% in women, from the 1960s to the 1970s, but this decreasing trend slowed from the 1970s to the 2000s. Among the stroke subtypes, ischemic stroke in both sexes and intracerebral hemorrhage in men showed a similar pattern. Stroke mortality decreased as a result of the decline in incidence and a significant improvement in survival rate. Although the incidence of acute myocardial infarction did not change in either sex, disease mortality declined slightly in women. From the 1960s to the 2000s, blood pressure control among hypertensive individuals improved significantly and the smoking rate decreased, but the prevalence of glucose intolerance, hypercholesterolemia, and obesity increased steeply.

Conclusions—Our findings suggest that in Japanese, the decreasing trends in the incidence of ischemic stroke have recently slowed down, and there has been no clear change in the incidence of acute myocardial infarction, probably because the benefits of hypertension control and smoking cessation have been negated by increasing metabolic risk factors. **(*Circulation*. 2013;128:1198-1205.)**

Key Words: coronary disease ■ incidence ■ mortality ■ stroke ■ trends

Cardiovascular disease (CVD), including stroke and coronary heart disease (CHD), is one of the leading causes of death worldwide.[1] Changes in lifestyle and advances in medical technology during the past half century have likely affected the prevalence of cardiovascular risk factors and thereby the incidence and mortality of CVD. According to vital statistics, Japanese populations were characterized by higher stroke mortality and lower CHD mortality than Western populations in the 1960s, and then stroke mortality in Japan began to decline in the 1970s.[1–3] However, the vital statistics based on death certificates cannot determine whether the secular change in mortality reflected a change in CVD incidence or the prevalence of its risk factors or an improvement in case fatality. In addition, diagnosis on death certificates is not always accurate[4] and is not based on standardized criteria. Therefore, population-based studies with standardized diagnostic criteria are needed to examine accurate trends in the incidence, mortality, and survival rate of CVD, as well as the prevalence of its risk factors.

Clinical Perspective on p 1205

Several population-based observational studies have examined the secular trends in CVD in Western[5–7] and Japanese populations[8–13]; however, there have been very few studies on CVD in Japan that have covered a period of multiple decades from the 1960s to the 2000s.[8] In our previous report from the Hisayama Study,[9] a long-term population-based prospective study in Japan, the incidence and mortality of stroke decreased significantly, but those of CHD did not show a clear secular change in either sex during the 40-year period from 1961 to 2000. For the present

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study, we extended the study period to 2009 and examined 5 cohorts, which were established in different years and were used to represent each decade from the 1960s to the 2000s. The aims of the present study were thus to provide an overview of the secular trends in the incidence, mortality, and survival rates of stroke and CHD along with the prevalence of risk factors during the past half century and to confirm whether or not the previously reported secular changes in CVD had continued into the most recent decade.

Methods

Study Cohorts

The town of Hisayama is located in a suburb of the Fukuoka metropolitan area in Kyushu, Japan. According to the national census, the population of the town was approximately 6500 in 1960 and 8400 in 2010, and the age and occupational distributions in the town have been very similar to those in the country of Japan as a whole (Figures I and II in the online-only Data Supplement). Since 1961, annual health examinations for residents of Hisayama aged ≥40 years have been repeated by the town government and Kyushu University to determine their health status. We attempted to examine >80% of the residents in this age group in health examinations every 2 to 5 years to establish new cohorts. In the present study, the examinations in 1961, 1974, 1983, 1993, and 2002 were used to establish 5 different cohorts. In 1961, 1658 residents aged ≥40 years participated in the examination (90% of the total population in this age group). Similarly, the number of participants was 2135 (participation rate, 81%) in 1974, 2551 (81%) in 1983, 2111 (53%) in 1993, and 3328 (78%) in 2002. After excluding those with a history of stroke or CHD, we established 5 cohorts consisting of 1618 participants in 1961, 2038 in 1974, 2459 in 1983, 1983 in 1993, and 3108 in 2002, and each cohort was followed up for 7 years (Figure III in the online-only Data Supplement). Consequently, these 5 cohorts roughly covered the decades of the 1960s, 1970s, 1980s, 1990s, and 2000s, respectively. The study was approved by the Kyushu University Institutional Review Board for Clinical Research.

Follow-Up Survey

Each cohort was followed up for 7 years by the annual health examinations or by mail or telephone for any participants who did not undergo the examination or who moved out of the town. The development of CVD was also checked by a daily monitoring system organized by the study team, local physicians, and the town government. All available information about potential CVD events and deaths among the study participants was collected and reviewed by physician members of the study to determine the occurrence of CVD events or cause of death under the standardized diagnostic criteria throughout the study period. When a participant died, autopsy was performed at the Department of Pathology of Kyushu University, if consent for autopsy was obtained. Our cohorts were characterized by extraordinarily high autopsy rates. During the 7-year follow-up period of each cohort, autopsy examination was performed for 181 (78%) of 232 deceased participants in the 1960s cohort, 165 (84%) of 196 in the 1970s cohort, 185 (84%) of 221 in the 1980s cohort, 156 (82%) of 190 in the 1990s cohort, and 170 (64%) of 267 in the 2000s cohort (Figure III in the online-only Data Supplement). The autopsy findings were used to adjudicate the underlying cause of death and confirm the existence of CVD (stroke lesions, myocardial necrosis, and atherosclerotic lesions in coronary, carotid, cerebral, and other major arteries) and to classify subtypes of stroke. Twenty-four participants (1%) in the 1990s cohort were lost to follow-up, and no participants in the other cohorts were lost to follow-up during the follow-up periods (Figure III in the online-only Data Supplement).

Risk Factors

Information on medical history, treatment of hypertension and diabetes mellitus, smoking habits, and alcohol intake was obtained by use of a standardized questionnaire. Smoking habits and alcohol intake were categorized as current use or not. Current smoking was defined as being when the participant smoked at least 1 cigarette per day. Current drinking was defined as when the participant drank at least 1 alcohol beverage per month. Blood pressure was measured in a supine position in 1961 and in a seated position in 1974, 1983, 1993, and 2002. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (average of 3 measurements) or the use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in participants with glycosuria in 1961, by fasting or postprandial plasma glucose concentrations in 1974 and 1983, and by a 75-g oral glucose tolerance test in 1993 and 2002, in addition to a medical history of or treatment for diabetes mellitus (online-only Data Supplement).[9,14–16] Serum total cholesterol concentrations were measured by the modified Zak-Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1983, 1993, and 2002.[9,14,17] Hypercholesterolemia was defined as serum total cholesterol levels ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured in light clothing without shoes, and obesity was defined as body mass index ≥25 kg/m^2.

Diagnostic Criteria for CVD

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours and was classified as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. The diagnosis of CHD included acute myocardial infarction, silent myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, and sudden cardiac death within 1 hour after the onset of acute illness. Acute myocardial infarction was diagnosed when a participant met at least 2 of the following 4 criteria: (1) Typical symptoms, including prolonged severe anterior chest pain; (2) evolving diagnostic ECG changes; (3) cardiac enzyme levels more than twice the upper limit of the normal range; and (4) morphological changes (local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy). Silent myocardial infarction was diagnosed for participants without any historical indication of clinical symptoms or abnormal cardiac enzyme changes by either of the following 2 criteria: (1) New onset of abnormal Q waves on ECG plus morphological myocardium changes (local asynergy on echocardiography or persistent perfusion defect on scintigraphy), or (2) myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. For participants who died, the underlying causes of death were classified as stroke, CHD, or others, using all available information such as autopsy examination, medical records, and death certificates. Deaths attributed to stroke and CHD were further classified as to their subtypes.

During the follow-up periods of the 5 cohorts, a total of 487 participants had first-ever stroke (344 ischemic stroke, 93 intracerebral hemorrhage, 45 subarachnoid hemorrhage, and 5 undetermined type) and a total of 208 participants had first-ever CHD. Among the 1106 deceased participants in total, 144 died of stroke (67 ischemic stroke, 48 intracerebral hemorrhage, 25 subarachnoid hemorrhage, and 4 undetermined type) and 61 died of CHD (Figure III in the online-only Data Supplement). Only 4 participants had no information for cause of death and were diagnosed as death of unknown cause.

Statistical Analysis

The prevalence of each risk factor was adjusted for age by the direct method and compared among the cohorts by logistic regression analysis. The World Health Organization standard population was used as a standard population for the age adjustment. The age-adjusted mean values of risk factors as continuous variables were calculated and compared by the linear regression model. Because the cohorts contained overlapping individuals, the logistic and linear regression analyses were fit by generalized estimating equations to account for individuals contributing to >1 examination. The incidence and mortality rates of CVD were calculated by the person-year method with adjustment for age by the direct method and compared by Poisson regression. Because individuals who developed CVD could not contribute to future cohorts, generalized estimating equations were not necessary in the analyses for incidence and mortality.[18] Participants who developed stroke or acute myocardial infarction were also followed up for the subsequent 5 years or to the end of the follow-up

period in each cohort, and survival curves were drawn with the Cox proportional hazards model with adjustment for age and sex. In each of the above-mentioned analyses, pairwise comparisons versus the 1960s cohort were adjusted for multiple comparisons by Dunnett test (for logistic, linear, and Poisson regression) or Bonferroni test (for the Cox model).

All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC). Two-sided values of $P<0.05$ were considered statistically significant.

Results

Trends in Cardiovascular Risk Factors

The age-adjusted prevalence or mean values of cardiovascular risk factors in the 5 baseline examinations are summarized in Table 1. The population grew 5 years older in both sexes over the period from 1961 to 2002. The prevalence of hypertension increased during the earlier period from 1961 to 1983 and then decreased during the subsequent period from 1983 to 2002, but these changes were not dramatic. The proportion of participants receiving antihypertensive treatment increased steeply and mean systolic blood pressure among hypertensive men and women decreased significantly over the study period. Consequently, mean systolic blood pressure among all participants decreased slightly in both sexes. In contrast, the prevalence of metabolic risk factors (ie, glucose intolerance, hypercholesterolemia, and obesity) increased with time in both sexes. The smoking rate in men and women decreased significantly from 1961 to 1993. The alcohol drinking rate increased slightly in men and steeply in women with time since 1974.

Trends in CVD Incidence

The age-adjusted incidence rates of stroke and CHD are compared among the 5 cohorts in Table 2. Stroke incidence decreased greatly, by 51% in men and by 43% in women, in the earlier period from the 1960s to the 1970s, but this decreasing trend slowed down in the subsequent period. A similar decreasing trend with a slowdown was observed in the incidence of ischemic stroke in both sexes. The incidence of intracerebral hemorrhage in men decreased consistently from the 1960s to the 1990s. The incidences of intracerebral hemorrhage in women and subarachnoid hemorrhage in both sexes showed no clear secular changes over the study period. Although CHD incidence in men did not show a significant secular change over the period, CHD incidence in women decreased significantly mainly in the recent period from the 1980s to the 2000s. However, the incidence of acute myocardial infarction did not decrease in either sex.

Age-specific incidence rates of stroke and acute myocardial infarction in the 5 cohorts are shown in Figure 1. Stroke incidence consistently decreased mainly in the aged group. In contrast, the incidence of acute myocardial infarction showed no clear secular changes among participants aged ≤79 years, whereas that in participants aged ≥80 years tended to increase from the 1960s to the 1980s and was unchanged thereafter.

Trends in CVD Survival

Participants who developed stroke or acute myocardial infarction during the 7-year period were further followed up for the subsequent 5 years (or to the end of the follow-up period) after the index events in each cohort. Figure 2 and Table I in the online-only Data Supplement demonstrate the estimated survival rates and hazard ratios for death over the 5 years after the onset of stroke or acute myocardial infarction, with adjustment for age and sex. The estimated 5-year survival rate of stroke improved greatly from the 1960s cohort (22.2%) to the 1980s cohort (55.3%) and improved slightly thereafter (63.0% in the 2000s cohort). Although the 5-year survival rate of acute myocardial infarction did not show a continuous improvement, probably because of the limited sample size, the survival rate in the 2000s cohort (61.2%) was significantly higher than that in the 1960s cohort (16.3%).

Trends in CVD Mortality

Age-adjusted mortality rates from stroke and CHD are compared among the 5 cohorts in Table 3. Stroke mortality in men and women decreased most in the earlier period from the 1960s to the 1970s, and this decreasing trend slowed down in the subsequent period. In regard to stroke subtypes, the mortality rate from ischemic stroke in both sexes decreased significantly over the study period, and the same was true for the mortality rate from intracerebral hemorrhage in men and that from subarachnoid hemorrhage in women. Although the mortality rates attributable to CHD and acute myocardial infarction in men did not show clear secular changes, in women they showed decreasing trends over the study period.

Discussion

Using the findings of 5 cohorts established in different decades in a Japanese community, we demonstrated that the decrease in stroke incidence and mortality in this community was most pronounced over the 1960s and 1970s, and then in the 3 more recent cohorts, the trend of decrease slowed. The incidence of acute myocardial infarction did not show clear secular changes in either sex, but mortality from acute myocardial infarction tended to decrease in women. From the 1960s to the 2000s cohort, blood pressure control among hypertensive individuals improved significantly and the prevalence of smoking decreased, whereas the prevalence of glucose intolerance, hypercholesterolemia, and obesity increased steeply. Changes in risk factors may have affected the trends in the risk of CVD during the past half century in Japanese.

Several population-based observational studies have examined secular trends in CVD in Japanese populations[8–13]; however, most of these studies have not covered very long periods of time.[10–13] The Akita-Osaka Study[8] recently reported secular trends in the incidence of stroke and CHD among middle-aged (40–69 years) men and women who lived in urban and rural communities in Japan over a 40-year period from 1964 to 2003. In that study, stroke incidence decreased significantly in both communities, which was in concordance with the present study. On the other hand, CHD incidence increased significantly among men in the urban community over the 1980s until the end of the study in 2003, which was different from our finding, probably because the Akita-Osaka Study did not include elderly people, who have a higher risk of CVD.

In the present study population, the prevalence of hypertension, one of the most powerful risk factors for CVD,[14,19] did not show a dramatic secular change. In contrast, average blood pressure levels in hypertensive individuals decreased continuously and greatly as a result of the spread of hypertension treatment. In addition, our

Table 1. Age-Adjusted Prevalence or Mean (SD) of Cardiovascular Risk Factors Among 5 Baseline Examinations of the Hisayama Study

	1961 (n=1618)	1974 (n=2038)	1983 (n=2459)	1993 (n=1983)	2002 (n=3108)	*P* for Trend
Men						
Number of participants	705	855	1048	747	1305	
Age, y	55 (11)	56 (11)	57 (11)*	61 (12)*	61 (12)*	<0.001
Hypertension, %	38.4	43.1*	47.7*	43.7*	41.3	0.71
Antihypertensive agents, %	2.0	8.4*	10.9*	14.7*	17.5*	<0.001
Systolic BP, mm Hg	136 (25)	139 (23)*	137 (19)	136 (18)	133 (20)*	<0.001
Diastolic BP, mm Hg	79 (14)	83 (12)*	84 (11)*	81 (10)*	81 (11)*	0.13
Systolic BP in hypertensive individuals, mm Hg	161 (20)	157 (20)*	152 (16)*	152 (16)*	148 (18)*	<0.001
Diastolic BP in hypertensive individuals, mm Hg	91 (13)	90 (11)	92 (9)	88 (10)*	89 (10)	0.01
Glucose intolerance, %	11.6	14.1	14.3*	29.9*	54.0*	<0.001
Hypercholesterolemia, %	2.8	12.2*	23.0*	25.2*	22.2*	<0.001
Total cholesterol, mmol/L	3.9 (0.9)	4.7 (0.8)*	5.0 (0.9)*	5.1 (0.8)*	5.1 (0.9)*	<0.001
Obesity, %	7.0	11.6*	20.2*	26.7*	29.2*	<0.001
Body mass index, kg/m^2	21.2 (2.3)	21.7 (2.3)*	22.3 (2.4)*	23.2 (2.1)*	23.4 (2.9)*	<0.001
Current smoker, %	75.0	73.3	57.2*	47.0*	47.4*	<0.001
Current drinker, %	69.6	63.8	65.2	64.6	71.8	0.004
Women						
Number of participants	913	1183	1411	1236	1803	
Age, y	57 (12)	58 (12)*	58 (12)	61 (13)*	62 (13)*	<0.001
Hypertension, %	35.9	40.1*	41.2*	34.6	30.8*	<0.001
Antihypertensive agents, %	2.1	7.4*	11.5*	15.2*	16.2*	<0.001
Systolic BP, mm Hg	137 (23)	139 (22)	136 (20)	135 (19)*	129 (20)*	<0.001
Diastolic BP, mm Hg	78 (12)	80 (11)*	80 (11)*	77 (10)*	76 (12)*	<0.001
Systolic BP in hypertensive individuals, mm Hg	163 (20)	161 (20)	155 (17)*	155 (17)*	149 (19)*	<0.001
Diastolic BP in hypertensive individuals, mm Hg	88 (11)	87 (11)	87 (9)	84 (10)*	86 (11)*	<0.001
Glucose intolerance, %	4.8	7.9*	7.0*	21.0*	35.1*	<0.001
Hypercholesterolemia, %	6.6	19.9*	33.5*	35.7*	35.3*	<0.001
Total cholesterol, mmol/L	4.2 (1.0)	5.0 (0.9)*	5.3 (1.0)*	5.5 (0.9)*	5.4 (0.9)*	<0.001
Obesity, %	12.9	21.5*	23.5*	26.2*	23.8*	<0.001
Body mass index, kg/m^2	21.6 (2.8)	22.4 (2.9)*	22.6 (2.7)*	23.0 (2.7)*	22.9 (3.5)*	<0.001
Current smoker, %	16.6	10.2*	7.4*	4.6*	8.5*	<0.001
Current drinker, %	8.3	5.7	7.8	12.9*	29.3*	<0.001

BP indicates blood pressure.
*P<0.05 compared with the examination in 1961 (after Dunnett test for multiple comparisons).

previous study reported that daily intake of salt among Hisayama residents showed a large reduction, from 18.3 g/d in 1965 to 9.8 g/d in 2004,[20] which was also likely to contribute to the reduction of blood pressure levels in the present study population. The incidence of ischemic stroke decreased with time, probably because of the improvement in hypertension management, the reduction in salt consumption, and the decreasing smoking rate. The reduction in the incidence of stroke and the improvement in its survival rate contributed to the decreasing trend in the stroke mortality. However, the decreasing trends in the incidence and mortality of ischemic stroke slowed down in recent years. One of the possible reasons for the slowdown is the increase in the prevalence of metabolic risk factors, which in turn is probably attributable to westernization of dietary habit and physical inactivity as a result of motorization. For example, the daily intake of total (and animal) fat showed a considerable increase, from 37.5 (11.4) g/d in 1965 to 52.3 (26.1) g/d in 2004, among Hisayama residents,[20] which was likely to have been the cause of the increasing prevalence of hypercholesterolemia and glucose intolerance. Glucose intolerance,[21] dyslipidemia,[17] obesity,[22] metabolic syndrome,[23] and underlying insulin resistance[24] are important risk factors for ischemic stroke in Japanese. Another reason may be that blood pressure control in hypertensive individuals was still not sufficient even in the latest examination, when the mean systolic

Table 2. Age-Adjusted Incidence (per 1000 Person-Years) of Stroke and Coronary Heart Disease Among 5 Cohorts of the Hisayama Study

	1960s Cohort (1961–1968)		1970s Cohort (1974–1981)		1980s Cohort (1983–1990)		1990s Cohort (1993–2000)		2000s cohort (2002–2009)		
	n	Incidence (95% CI)	n	Incidence (95% CI)	n	Incidence (95% CI)	n	Incidence (95% CI)	n	Incidence (95% CI)	*P* for Trend
Men											
Stroke	67	14.34 (10.60–18.08)	39	6.99* (4.52–9.47)	45	5.45* (3.83–7.07)	31	4.38* (1.94–6.82)	53	4.22* (3.05–5.40)	<0.001
Ischemic	41	9.50 (6.26–12.75)	31	5.61* (3.34–7.88)	36	4.33* (2.89–5.76)	22	2.51* (1.37–3.65)	34	2.70* (1.77–3.63)	<0.001
ICH	20	3.75 (2.10–5.41)	8	1.38* (0.40–2.36)	8	1.00* (0.29–1.72)	6	0.58* (0.12–1.04)	14	1.04* (0.48–1.61)	<0.001
SAH	4	0.70 (0.01–1.38)	0	0.00	1	0.12 (0.00–0.35)	3	1.29 (0.00–3.40)	4	0.41 (0.00–0.81)	0.87
Undetermined	2	0.38 (0.00–0.92)	0	0.00	0	0.00	0	0.00	1	0.07 (0.00–0.22)	0.20
CHD	17	3.59 (1.74–5.44)	16	4.05 (1.53–6.58)	24	2.74 (1.63–3.86)	21	3.27 (0.94–5.60)	45	3.20 (2.23–4.17)	0.91
AMI	8	1.93 (0.44–3.42)	8	2.30 (0.25–4.35)	14	1.51 (0.72–2.30)	7	0.73 (0.19–1.28)	21	1.44 (0.80–2.08)	0.90
Women											
Stroke	50	7.19 (5.16–9.21)	45	4.07* (2.87–5.26)	55	4.29* (3.14–5.44)	52	3.76* (2.63–4.90)	50	2.12* (1.50–2.75)	<0.001
Ischemic	37	5.31 (3.57–7.04)	32	2.87* (1.87–3.87)	39	2.99* (2.04–3.95)	38	2.75* (1.77–3.74)	34	1.45* (0.93–1.98)	<0.001
ICH	5	0.78 (0.08–1.48)	5	0.48 (0.06–0.90)	9	0.69 (0.24–1.15)	10	0.64 (0.23–1.05)	8	0.35 (0.10–0.60)	0.40
SAH	6	0.84 (0.17–1.51)	8	0.72 (0.22–1.22)	7	0.60 (0.14–1.06)	4	0.37 (0.00–0.76)	8	0.32 (0.09–0.56)	0.05
Undetermined	2	0.27 (0.00–0.64)	0	0.00	0	0.00	0	0.00	0	0.00	>0.99
CHD	10	1.31 (0.50–2.12)	15	1.25 (0.62–1.89)	20	1.49 (0.83–2.15)	20	1.12 (0.61–1.63)	20	0.80 (0.41–1.18)	0.04
AMI	6	0.78 (0.16–1.41)	7	0.57 (0.15–0.99)	12	0.93 (0.40–1.46)	9	0.52 (0.16–0.87)	13	0.50 (0.21–0.79)	0.23

AMI indicates acute myocardial infarction; CHD, coronary heart disease; CI, confidence interval; ICH, intracerebral hemorrhage; n, number of events; and SAH, subarachnoid hemorrhage.

*$P<0.05$ compared with the 1960s cohort (after Dunnett test for multiple comparisons).

blood pressure among hypertensive individuals was higher than 140 mm Hg, which suggests that most hypertensive subjects did not achieve the target blood pressure level recommended by the clinical guidelines for hypertension.[25–27]

Although a decrease in the incidence and mortality of intracerebral hemorrhage was seen in men and was likely attributable to the improvement in hypertension management, a comparable trend of decrease was not seen in women, probably because of the small number of events. In addition, our previous study suggested that alcohol consumption and hypertension synergistically increased the risk of intracerebral hemorrhage.[28] Because the drinking rate in women was much lower than that in men over the study period, the impact of hypertension on the development of intracerebral hemorrhage may be smaller in women.

The incidence of acute myocardial infarction did not show a clear change in either sex, probably because the increasing prevalence of metabolic risk factors negated the benefit of improvement in hypertension control. The incidence of total CHD decreased recently in women, which suggests that the incidence of silent myocardial infarction showed a decreasing trend in women. However, accurate diagnosis of silent myocardial infarction is difficult because it depends on the findings of autopsy and clinical examinations of cases without any history of acute episodes. Therefore, the incidence of total CHD might have been underestimated, especially in the 2000s cohort. Mortality from acute myocardial infarction and CHD in women showed decreasing trends as a result of the improvements in postevent survival rates. In contrast, mortality from acute myocardial infarction and CHD in men showed no clear secular change. This sex difference may be explained by the much higher smoking rate in men than in women.

In the present study population, the incidence of acute myocardial infarction in very elderly subjects (aged ≥80 years) increased with time during the earlier period from the 1960s to the 1980s. The decrease in stroke mortality, the most common type of CVD in Japanese, might contribute to the longevity of

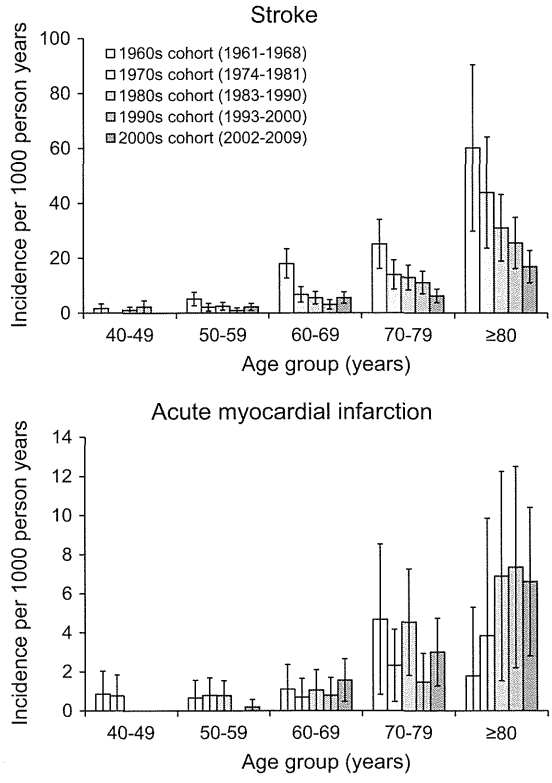

Figure 1. Age-specific incidence of stroke (**top**) and acute myocardial infarction (**bottom**) with adjustment for sex, among 5 cohorts of the Hisayama Study. Bars indicate 95% confidence intervals.

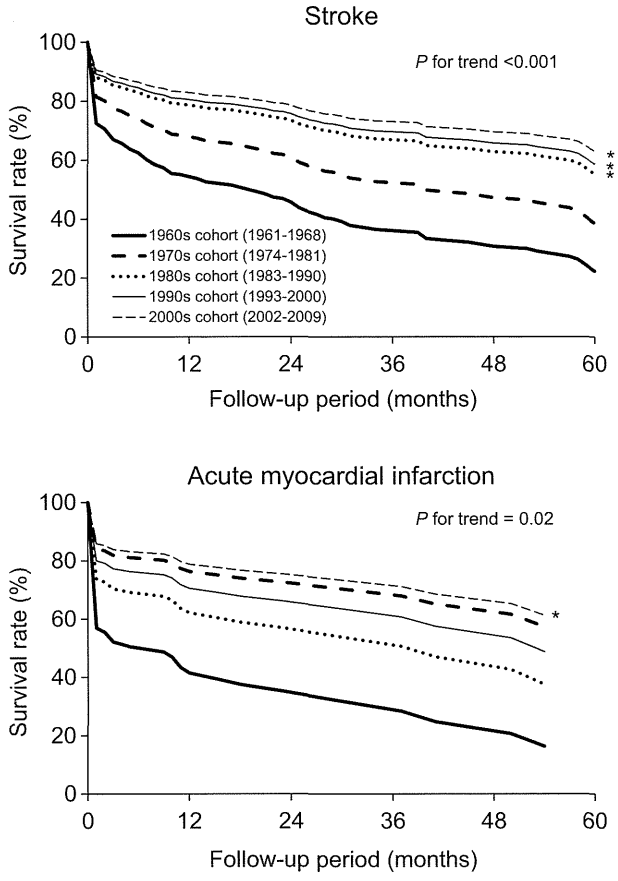

Figure 2. Age- and sex-adjusted 5-year survival curves after the onset of stroke (**top**) and acute myocardial infarction (**bottom**) among 5 cohorts of the Hisayama Study. *P<0.05 compared with 1960s cohort (after Bonferroni correction for multiple comparisons).

people with atherosclerosis, and these elderly subjects with relatively severe atherosclerosis might have a higher risk of other atherosclerotic disease, such as myocardial infarction. This increase in the incidence of acute myocardial infarction in the elderly has come to a stop since the 1980s, possibly in association with the slowdown of the decrease in the stroke mortality.

The present study was the first to examine the incidence, mortality, and survival rates of stroke and CHD over the past half century in a Japanese population that included both middle-aged and elderly participants. The follow-up of each cohort was almost complete. The methods for case ascertainment and the diagnostic criteria of CVD were consistent throughout the study period. All CVD events and causes of death were adjudicated by a panel of study physicians, and the presence of CVD lesions was morphologically confirmed by autopsy in most of the deceased subjects. Although the remarkable improvement in diagnostic techniques over the past half century might have resulted in information bias in diagnosis, the possibility of misclassification in CVD diagnosis was minimized by these study features. However, there are some issues to be discussed. First, because the diagnostic methods for glucose intolerance were different among the cohorts, the prevalence of glucose intolerance might be underestimated in the earlier cohorts. Second, the methods for measurement of serum total cholesterol were different among the cohorts, and the cholesterol values were not calibrated among the different methods. Third, socioeconomic information such as education level and occupation, which might be associated with the incidence and mortality of CVD, was not available in the present cohorts. Finally, it is generally agreed that an acceptable participation rate in a population-based study (ie, a rate that practically eliminates the threat of selection bias attributable to nonparticipants) is >70% of the target population.[29,30] Therefore, we attempted to recruit >80% of residents to the town's health examinations. However, the participation rate of the health examination in 1993 (53%) was lower than that in the other 4 examinations (≥78%), and this might have increased the risk of selection bias in the 1990s cohort. As a possible reason for this low participation rate in 1993, every employee in Japan has been required, starting in 1988 (Industrial Safety and Health Act), to have a medical examination at their place of employment. Thus, employed residents tended not to participate in the town's health examination during the 1990s. However, our main conclusions did not change substantially when we applied a cohort based on the health examination in 1988 (participation rate, 81%) instead of the examinations in 1983 and 1993 (data not shown).

In conclusion, the incidence and mortality of ischemic stroke in both sexes and intracerebral hemorrhage in men declined as a result of the improvement of hypertension management or the reduction in the smoking rate. However, blood pressure control in hypertensive participants is still insufficient, and the smoking rate in men is still much higher than in Western populations.[31] In addition, the decreasing trends in the incidence of ischemic stroke slowed down recently, and there was no clear change in the incidence of acute myocardial infarction, probably because of the increasing metabolic

Table 3. Age-Adjusted Mortality (per 1000 Person-Years) of Stroke and Coronary Heart Disease Among 5 Cohorts of the Hisayama Study

	1960s Cohort (1961–1968)		1970s Cohort (1974–1981)		1980s Cohort (1983–1990)		1990s Cohort (1993–2000)		2000s Cohort (2002–2009)		
	n	Mortality (95% CI)	n	Mortality (95% CI)	n	Mortality (95% CI)	n	Mortality (95% CI)	n	Mortality (95% CI)	*P* for Trend
Men											
Stroke	36	6.96 (4.55–9.38)	10	2.15* (0.59–3.71)	13	1.70* (0.75–2.65)	4	0.40* (0.01–0.79)	8	0.61* (0.17–1.06)	<0.001
Ischemic	11	2.49 (0.84–4.13)	5	1.32 (0.00–2.70)	10	1.24 (0.45–2.03)	1	0.09* (0.00–0.27)	4	0.28* (0.01–0.55)	<0.001
ICH	19	3.44 (1.88–5.00)	4	0.69* (0.01–1.37)	2	0.34* (0.00–0.81)	1	0.10* (0.00–0.28)	2	0.11* (0.00–0.26)	<0.001
SAH	4	0.67 (0.01–1.32)	0	0.00	1	0.12 (0.00–0.35)	2	0.21 (0.00–0.50)	2	0.23 (0.00–0.55)	0.20
Undetermined	2	0.37 (0.00–0.89)	1	0.13 (0.00–0.39)	0	0.00	0	0.00	0	0.00*	0.07
CHD	5	0.85 (0.10–1.60)	6	0.88 (0.16–1.60)	5	0.58 (0.06–1.10)	4	0.42 (0.01–0.84)	10	0.64 (0.24–1.05)	0.26
AMI	4	0.69 (0.01–1.37)	1	0.20 (0.00–0.59)	2	0.20 (0.00–0.48)	3	0.32 (0.00–0.69)	5	0.30 (0.03–0.57)	0.40
Women											
Stroke	21	3.20 (1.79–4.61)	17	1.45 (0.76–2.14)	11	0.82* (0.32–1.31)	12	0.85* (0.34–1.37)	12	0.37* (0.16–0.59)	<0.001
Ischemic	11	1.79 (0.70–2.88)	9	0.76 (0.26–1.25)	6	0.40* (0.08–0.73)	4	0.34* (0.00–0.70)	6	0.20* (0.03–0.36)	<0.001
ICH	5	0.75 (0.08–1.42)	4	0.34 (0.01–0.68)	1	0.07 (0.00–0.19)	6	0.37 (0.06–0.67)	4	0.11 (0.00–0.22)	0.06
SAH	4	0.53 (0.01–1.06)	4	0.35 (0.00–0.70)	4	0.35 (0.00–0.70)	2	0.15 (0.00–0.36)	2	0.06 (0.00–0.15)	0.02
Undetermined	1	0.13 (0.00–0.38)	0	0.00	0	0.00	0	0.00	0	0.00	>0.99
CHD	5	0.65 (0.08–1.21)	6	0.49 (0.10–0.88)	9	0.64 (0.22–1.05)	6	0.29 (0.05–0.52)	5	0.16 (0.01–0.32)	0.009
AMI	4	0.52 (0.01–1.03)	3	0.25 (0.00–0.53)	4	0.31 (0.00–0.61)	5	0.22 (0.02–0.42)	4	0.11 (0.00–0.21)	0.06

AMI indicates acute myocardial infarction; CHD, coronary heart disease; CI, confidence interval; ICH, intracerebral hemorrhage; n, number of events; and SAH, subarachnoid hemorrhage.

*$P<0.05$ compared with the 1960s cohort (after Dunnett test for multiple comparisons).

risk factors. The intensive management of metabolic risk factors and best efforts to reduce the smoking rate and to achieve strict blood pressure control are needed for further prevention of CVD in Japanese.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The Japanese population has been characterized by a higher incidence and mortality of stroke and a lower incidence and mortality of coronary heart disease than Western populations; however, the recent westernization of lifestyle and advances in medical technology are likely to have affected the incidence and mortality of these diseases in Japan. Using data from 5 cohorts established in different decades over the past half century by the Hisayama Study, a prospective cohort study of cardiovascular disease in Japan, we showed that the incidence and mortality of stroke decreased greatly from the 1960s to the 1970s, but this decreasing trend slowed down recently. In contrast, the incidence of acute myocardial infarction did not show a clear secular change. These trends were likely to be associated with secular changes in cardiovascular risk factors. Although the improvement in hypertension management and the decrease in smoking rate contributed to a decline in stroke incidence, most hypertensive subjects did not achieve a guideline-recommended target blood pressure level of 140/90 mm Hg even in the recent examination in 2002, and smoking rates in men were still much higher than in Western populations. In addition, the increasing rates of metabolic risk factors, such as diabetes mellitus, dyslipidemia, and obesity, are currently the greatest concern, because they may increase the incidence of cardiovascular disease in the near future. Our study suggests that strict blood pressure control, smoking cessation, and intensive management of metabolic risk factors are needed for further prevention of cardiovascular disease in Japan.