Trends in the Incidence, Mortality, and Survival Rate of Cardiovascular Disease in a Japanese Community
The Hisayama Study

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Background and Purpose—The slowdown of a steeply declining trend in cardiovascular mortality has been reported in Japan, but precise reasons for this trend are uncertain.

Methods—We established 3 study cohorts of Hisayama residents aged ≥40 years without a history of stroke or myocardial infarction in 1961 (1618 subjects, first cohort), 1974 (2038 subjects, second cohort), and 1988 (2637 subjects, third cohort). We followed up with each cohort for 12 years, comparing the incidence, mortality, and survival rate of cardiovascular disease.

Results—The age-adjusted incidence of cerebral infarction significantly declined by 37% for men and by 32% for women from the first to the second cohort. It continued to decline by 29% for men, but the decline decelerated for women in the third cohort. The incidence of cerebral hemorrhage steeply declined by 61% from the first to the second cohort in men only, while it was sustained for both sexes in the third cohort. Stroke mortality continuously declined as a result of these incidence changes and significant improvement of survival. In contrast, the incidence and mortality rate of coronary heart disease were unchanged except for the increasing incidence in the elderly. The prevalence of severe hypertension and current smoking significantly decreased, while that of glucose intolerance, hypercholesterolemia, and obesity greatly increased among the cohorts.

Conclusions—Our data suggest that the decline in stroke incidence is slowing down and that the incidence of coronary heart disease has been increasing in the elderly in recent years. Insufficient control of hypertension and the increase in metabolic disorders may contribute to these trends. (Stroke. 2003;34:2349-2354.)

Key Words: coronary heart disease ■ incidence ■ mortality ■ secular trend ■ stroke

According to world vital statistics in the 1950s and 1960s, the Japanese were characterized by the highest stroke mortality and by a lower coronary heart disease (CHD) mortality compared with Western populations.1–4 In Japan, the stroke mortality rate started to decline steeply in the 1970s, but the slowdown of this decline has been reported in recent years.1,2 However, vital statistics are not always accurate with regard to the cause of death listed on death certificates.5 It is also difficult to know precise trends in mild cases of cardiovascular disease (CVD), and it is not possible to know whether these trends reflect a changing incidence or an improvement of case fatality rate. These facts imply that population-based studies collecting CVD incidence data are needed to elucidate secular trends.

Most previous epidemiological studies have examined CVD incidence trends by comparing prevalence rates of hospitalized cases among different time periods in registration studies6–9 or by dividing a long-term follow-up period into several parts in cohort studies.10,11 These methods, however, are potentially biased by the improvement of diagnostic techniques and by changes in the characteristics of the study subjects. The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) Project is a well-performed epidemiological study that examined CVD incidence and mortality trends from 37 populations in 21 countries; however, it did not include Japan.12 The Hisayama Study is a population-based study that has established 3 study cohorts at times corresponding to periods of remarkable lifestyle changes in Japan.13–15 In this study, study team physicians performed physical examinations of those subjects who developed CVD and collected detailed clinical information about them. Furthermore, morphological examinations were performed in most of the CVD cases in each cohort.16 These characteristics of the study design provide us with an opportunity to determine secular trends in cardiovascular incidence and mortality with a high degree of accuracy.
Subjects and Methods

Study Population
Hisayama Town is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for many years (annual variation rate <5%) and has been shown to be representative of Japan as a whole on the basis of data from the national census. The study design and characteristics of the subject population have been described in detail elsewhere. Briefly, we established 3 study cohorts from Hisayama residents aged ≥40 years in 1961, 1974, and 1988 after screening examinations. In 1961, a total of 1658 residents in that age group consented to participate in the screening examination (participation rate, 90.1%). After the exclusion of 28 subjects with a history of CVD and 12 subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. In the same manner, we established the second cohort consisting of 2038 subjects from 2135 participants (participation rate, 81.2%) in 1974 and the third cohort of 2637 subjects from 2742 participants (participation rate, 80.9%) in 1988.

Follow-Up
The cohort populations have been undergoing longitudinal observations by repeated health examinations. Health status was checked every year by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. When the subjects died, autopsy examinations were performed at the Department of Pathology of Kyushu University. During the 12-year follow-up period of each cohort, autopsy examinations were performed on 327 subjects (81.6% of the deceased subjects) in the first cohort, 342 subjects (86.2%) in the second cohort, and 366 subjects (75.5%) in the third cohort. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up.

Definition of Cardiovascular Events
The diagnosis of stroke was determined on the basis of clinical information and autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours and was classified as either cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. Subjects who died within 24 hours after the onset of the symptoms and had evidence of stroke were also included as stroke cases.

The diagnosis of CHD included acute myocardial infarction (MI), silent MI, and sudden cardiac death within 1 hour after the onset of acute illness. The diagnosis of MI was made on the basis of clinical symptoms, ECG recordings, cardiac enzymes, and morphological changes. Acute MI was diagnosed when the suspected subject met at least 2 of the following criteria: (1) typical symptoms including prolonged severe chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic ECG changes; and (4) morphological changes including 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 MI was defined as myocardial scars without any information indicated in the history regarding clinical symptoms or abnormal cardiac enzyme changes. Cases experiencing MI during surgery or during a cardiac intervention procedure were excluded.

We gathered all available information about potential cardiovascular events and death among the study participants. All these materials were reviewed by a panel of physician members of the Hisayama Study to determine the occurrence of CVD and/or cause of death under the standard criteria throughout the study period.

Risk Factors
Recumbent blood pressures were measured at every examination, and hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. Blood pressures were also categorized as normal (<130/85 mm Hg), high-normal (<140/90 mm Hg), stage 1 (<160/100 mm Hg), stage 2 (<180/110 mm Hg), and stage 3 (≥180/110 mm Hg). Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988. In addition to medical history of diabetes. Serum cholesterol levels were measured by the modified Zak-Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988. Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L. 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 standard questionnaire and was categorized as current habitual use or not. Subjects who reported smoking at least 1 cigarette per day were defined as current smokers, and subjects who reported consuming alcohol at least once a month were regarded as current drinkers.

Statistical Analysis
We counted only first-ever cardiovascular events in this study. The CVD incidence and mortality rates were calculated by the person-year method and adjusted for the age distribution of the world standard population by the direct method. The differences in the incidence and mortality among 3 cohorts were tested by sex with the use of the Cox proportional hazards model after adjustment for age. Subjects who developed cardiovascular events were also followed up for the subsequent 5 years or to the end of the follow-up in every cohort, and survival rates were estimated with the Cox proportional hazards model. The significance of risk factor trends was examined with the χ² test. All statistical analyses were performed with the SAS program package. P<0.05 was considered statistically significant in all analyses.

Results

Trends in CVD Risk Factors
We compared the prevalence of cardiovascular risk factors at the baseline examination among the 3 study cohorts by sex (Table 1). In both sexes, the prevalence of hypertension was not different among the cohorts, but the proportion of individuals using antihypertensive agents consistently increased with time. When we compared blood pressure levels among the cohorts, the proportion of subjects with stage 2 and 3 hypertension declined, while that of subjects with stage 1 hypertension increased in both sexes. The prevalence of glucose intolerance, hypercholesterolemia, and obesity increased progressively with time. The proportion of current smokers in both sexes and that of male drinkers declined linearly over the cohorts.

Trends in CVD incidence
The age-adjusted stroke incidence significantly declined by 48% for men (P<0.01) and tended to decline by 25% for women (P=0.06) from the first to the second cohort, but this declining trend was slowed in the third cohort (Table 2). The age-adjusted incidence of cerebral infarction for men significantly declined throughout the cohorts. For women, the incidence also declined from the first to the second cohort, but the decline decelerated in the third cohort. The age-adjusted incidence of cerebral hemorrhage for men significantly declined by 61% from the first to the second cohort but remained unchanged in the third cohort. The age-adjusted incidence of cerebral hemorrhage for women and that of subarachnoid hemorrhage for both sexes were constant among the cohorts.

The age-adjusted incidence of CHD did not significantly change throughout the cohorts for either sex. The age-adjusted incidence of acute MI, silent MI, and sudden death also did not significantly change among the cohorts.
Trends in Age-Specific CVD Incidence

The age-specific incidence rates of CVD for men and women combined among the 3 cohorts are shown in Figure 1. The incidence of cerebral infarction consistently decreased mainly in the aged subjects. The incidence of cerebral hemorrhage in the subjects aged 80 years greatly decreased from the first to the second cohort, but it showed no further change in the third cohort. In contrast, the incidence of cerebral hemorrhage in the subjects aged 80 years continuously increased. The incidence of CHD showed no significant trend among subjects aged <80 years, while it tended to increase in the oldest age group.

Trends in CVD Survival

Age- and sex-adjusted 5-year survival curves after CVD events are shown in Figure 2. The 5-year survival after cerebral infarction significantly improved from the first (40%) to the third cohort (61%). The 5-year survival after cerebral hemorrhage greatly increased from 3% to 55%, mainly as a result of the improvement of the 1-month survival. A pattern similar to that of cerebral hemorrhage was observed for subarachnoid hemorrhage, but the differences were not significant. The 5-year survival after acute MI significantly improved from the first to the second cohort (18% to 32%, respectively) but remained constant in the third cohort (63%).

Trends in CVD Mortality

The age-adjusted stroke mortality significantly declined from the first to the third cohort for both sexes (Table 3). The age-adjusted mortality as a result of cerebral infarction for both sexes and that of cerebral hemorrhage for men linearly

### TABLE 1. Prevalence by Sex of Cardiovascular Risk Factors at Baseline Among 3 Cohorts in 1961, 1974, and 1988 (the Hisayama Study)

<table>
<thead>
<tr>
<th>Variables</th>
<th>1st Cohort (n=705)</th>
<th>2nd Cohort (n=855)</th>
<th>3rd Cohort (n=1110)</th>
<th>P for Trend</th>
<th>1st Cohort (n=913)</th>
<th>2nd Cohort (n=1183)</th>
<th>3rd Cohort (n=1527)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±11</td>
<td>56±11</td>
<td>57±12</td>
<td>&lt;0.001</td>
<td>57±12</td>
<td>58±12</td>
<td>59±12</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38.6</td>
<td>40.4</td>
<td>41.5</td>
<td>0.22</td>
<td>37.4</td>
<td>44.0</td>
<td>38.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Antihypertensive agents, %</td>
<td>2.1</td>
<td>8.5</td>
<td>14.3</td>
<td>0.001</td>
<td>2.2</td>
<td>8.3</td>
<td>15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood pressure category, %</td>
<td></td>
<td></td>
<td></td>
<td>0.052</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>48.4</td>
<td>44.7</td>
<td>43.7</td>
<td></td>
<td>48.5</td>
<td>41.6</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>High-normal</td>
<td>13.3</td>
<td>16.6</td>
<td>19.6</td>
<td></td>
<td>14.4</td>
<td>15.2</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>19.2</td>
<td>22.7</td>
<td>25.5</td>
<td></td>
<td>19.3</td>
<td>23.7</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>10.6</td>
<td>9.7</td>
<td>8.6</td>
<td></td>
<td>11.0</td>
<td>12.3</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>8.5</td>
<td>6.3</td>
<td>2.6</td>
<td></td>
<td>6.9</td>
<td>7.3</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Glucose intolerance, %</td>
<td>12.1</td>
<td>13.8</td>
<td>31.9</td>
<td>0.001</td>
<td>4.8</td>
<td>8.1</td>
<td>27.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>1.7</td>
<td>5.3</td>
<td>14.9</td>
<td>0.001</td>
<td>3.2</td>
<td>9.6</td>
<td>25.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>7.4</td>
<td>11.6</td>
<td>23.2</td>
<td>0.001</td>
<td>12.9</td>
<td>20.8</td>
<td>23.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>76.3</td>
<td>73.0</td>
<td>49.9</td>
<td>0.001</td>
<td>16.8</td>
<td>10.7</td>
<td>6.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Current drinker, %</td>
<td>69.4</td>
<td>64.0</td>
<td>60.2</td>
<td>0.001</td>
<td>8.3</td>
<td>5.6</td>
<td>8.7</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or a current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥240 mg/dL. Obesity was defined as body mass index ≥25.0 kg/m².

### TABLE 2. Age-Standardized Incidence Rate (per 100 000 Person-Years) of Cardiovascular Disease Among 3 Cohorts of the Hisayama Study by Sex, With a 12-Year Follow-Up in Each Cohort

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>97</td>
<td>73</td>
<td>86</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>63</td>
<td>59*</td>
<td>60†</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>27</td>
<td>14*</td>
<td>20</td>
<td>0.001</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>Undetermined</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>25</td>
<td>32</td>
<td>56</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>0.001</td>
</tr>
<tr>
<td>Silent myocardial infarction</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>0.001</td>
</tr>
<tr>
<td>Sudden death</td>
<td>2</td>
<td>5</td>
<td>14</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*P<0.05 vs 1st cohort; †P<0.05 vs 2nd cohort. 95% confidence intervals are shown in parentheses.
declined throughout the study period. The age-adjusted mortality from subarachnoid hemorrhage and that from CHD did not significantly change among the cohorts for either sex.

**Discussion**

By comparing the incidence, mortality, and survival rates of CVD among 3 cohorts established at different times in a Japanese community, we demonstrated that stroke incidence significantly declined from the first to the second cohort but that a slowdown of this declining trend was observed in the third cohort. In contrast, CHD incidence and mortality remained low and showed no apparent secular trend. Changes in risk factors, namely, the improvement of hypertension control and the increase in metabolic disorders, may have affected these trends. Another striking finding is that the incidence of cerebral hemorrhage and CHD, contrary to that of cerebral infarction, increased with time in very old subjects.

Hypertension is a strong risk factor for cerebral infarction. During the study period, the prevalence of hypertension remained stable, but the blood pressure level significantly decreased as a result of the 7-fold increment in the use of antihypertensive medication. This apparently resulted in a reduction in the incidence of cerebral infarction. However, despite continuing improvement in hypertension management, the decline in the incidence of cerebral infarction slowed down in the third cohort. One of the probable reasons is the steep increase in obesity, hyperlipidemia, and diabetes, which significantly increase the risk of cerebral infarction. Another reason may be that two thirds of the hypertensives have not yet received antihypertensive medication, and one fourth of the hypertensives still have stage 2 or 3 hypertension.

The incidence of cerebral hemorrhage was unchanged except for the steeply declining incidence from the first to the second cohort in men. Our previous report showed that heavy alcohol consumption led to a great increase in the risk of...
Control of hypertension diminished this synergistic effect and resulted in this steeply declining trend in men. Despite the improvement of hypertension management, the incidence of cerebral hemorrhage remained stable in the third cohort. The precise reasons for this trend are unknown, but the aforementioned insufficient control of hypertension and the increasing incidence in the elderly subjects may contribute to this trend.

In contrast to the dynamic changes in stroke incidence, CHD incidence remained low and showed no apparent secular change. It is well known that hypertension, smoking, and hyperlipidemia are important risk factors for CHD; however, the prevalence of hyperlipidemia was low, and its impact on CHD was much weaker in Japanese than in Western populations. Moreover, the increase in metabolic disorders may negate the beneficial effects of secular improvement of hypertension control and the decreasing prevalence of smoking habits.

In our population, the incidence of CHD and cerebral hemorrhage in very old subjects increased with time. The decreased incidence and mortality of cerebral infarction, the most common type of CVD in Japanese, may contribute to the longevity of persons with atherosclerosis. It is reasonable to think that these elderly subjects with relatively severe atherosclerosis had a higher risk of other atherosclerotic disease, such as CHD and cerebral hemorrhage.

There are several points to remember when the results of our study are interpreted. First, the method for diagnosing CVD was changed remarkably by the improvement of diagnostic techniques, and this may affect the incidence rate. In our study, however, methods for case ascertainment and diagnostic criteria of CVD were consistent throughout the study period. Moreover, the presence and type of CVD were confirmed by morphological examinations in most of the deceased subjects throughout the study period. Second, we established 3 cohorts independently in the same manner, but the subjects in later cohorts included many survivors of the former cohorts. This may affect the development of CVD; however, we enrolled most of the unselected residents in every cohort (participation rate >80%), and the prevalence rate of cardiovascular risk factors in the third cohort was similar to those of the national survey on circulatory disorders and the national dietary survey of Japan conducted during the same time period (data not shown). Third, the criteria for glucose intolerance were different among cohorts, suggesting an underestimation of its prevalence in the former cohorts. Fourth, there were a small number of CVD cases in each cohort, indicating a larger chance of bias in its trends. Nonetheless, we believe that the findings of our study represent precise secular trends, since we performed this study using a highly accurate method for determining all cardiovascular events.

In conclusion, in a Japanese population, stroke incidence and mortality declined markedly between the 1960s and 1970s, mainly as a result of the improvement of hypertension management. However, the increase in metabolic disorders and insufficient control of hypertension slowed this declining trend in the late 1980s and 1990s. These changes in risk factors also contributed to the lowered and sustained low incidence and mortality of CHD. In addition to strict hypertension management, urgent care for metabolic disorders is needed for further prevention of CVD in Japan.

Acknowledgments
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References


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